NATPARA® (rhPTH[1-84]) FOR INJECTION: A REPLACEMENT FOR ENDOGENOUS PARATHYROID HORMONE(1-84) FOR THE LONG TERM TREATMENT OF HYPOPARATHYROIDISM

BRIEFING DOCUMENT FOR THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

$1,25(OH)_2D$	1,25-dihydroxyvitamin D, active vitamin D
25(OH) D	25-hydroxyvitamin D, native vitamin D
ACSC	Albumin-corrected total serum calcium
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALX1-11	Recombinant human parathyroid hormone (full-length, amino acids 1-84), the first compound code for rhPTH(1-84)
ANCOVA	Analysis of covariance
AUC	Area under the curve
BLA	Biologic License Application
BMD	Bone mineral density
BMI	Body mass index
BSAP	Bone-specific alkaline phosphatase
BTM	Bone turnover marker
BUN	Blood urea nitrogen
CaSR	Calcium-sensing receptor
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CrCl	Creatinine clearance
DNA	Deoxyribonucleic acid
DXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
E. coli	*Escherichia coli*
ECP	*Escherichia coli* protein or *E. coli* protein
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration
FOH	Focal osteoblast hyperplasia
GI	Gastrointestinal
HCP	Healthcare professional
HR	Heart rate
IIT	Investigator-initiated Trial
IND	Investigational New Drug Application
ITT	Intent-to-Treat
IV	Intravenous
L1-L4	Lumbar vertebra 1 through 4
LLN	Lower limit of normal reference range
LS Mean	Least square mean

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

MedDRA	Medical Dictionary for Regulatory Activities
Natpara®	NPSP558, a Recombinant Human Parathyroid Hormone – rhPTH(1-84)
NPS	NPS Pharmaceuticals, Inc.
NPSP558	Natpara®, a Recombinant Human Parathyroid Hormone – rhPTH(1-84)
OR	Odds ratio
P1NP	Procollagen Type 1 amino-terminal propeptide
PD	Pharmacodynamics
PR	In electrocardiography, the time from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex
PT	Preferred term
PTH	Parathyroid hormone
QD	Once daily
QoL	Quality of Life
QRS	The QRS complex represents the time it takes for depolarization of the ventricles
QT	The time from the beginning of the QRS complex to the end of the T wave
QTcF	QT corrected for heart rate by the Fridericia method
RACE	Natpara Study PAR-C10-008
RELAY	Natpara Study PAR-C10-007
REPEAT	Natpara Study PAR-C10-009
REPLACE	Natpara Study CL1-11-040
rhPTH(1-84)	Recombinant human parathyroid hormone (1-84)
rhPTH(1-34)	Recombinant human parathyroid hormone (1-34), teriparatide
SAE	Serious adverse event
SC	Subcutaneous
s-CTx	Serum carboxy-terminal telopeptide of type I collagen
SD	Standard deviation
SF-36	Short form-36 questionnaire
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal range
US	United States
WBC	White blood cell

1 EXECUTIVE SUMMARY

Hypoparathyroidism is a rare disease that results from deficiency or absence of parathyroid hormone (PTH). Hypoparathyroidism is the last of the classic endocrine disorders to not have an approved hormone replacement therapy. Untreated or inadequately treated hypoparathyroidism leads to clinically significant metabolic sequelae including hypocalcemia, which when severe is life-threatening. Current management consists of pharmacological doses of calcium and active vitamin D to manage hypocalcemia. While this current treatment approach is intended to maintain serum calcium and minimize the symptoms of hypocalcemia, it does not address the physiologic aspects of hypoparathyroidism including lack of endogenous 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) production, hypercalciuria, hyperphosphatemia, and metabolic bone abnormalities. Oral calcium and active vitamin D do not correct the underlying PTH deficiency and are associated with several challenges, including long-term complications from the use of these supplements without the underlying PTH hormone, which contributes to renal function deterioration, renal stones, and soft tissue calcifications.

NPS Pharmaceuticals, Inc. (hereafter NPS) developed recombinant human PTH – rhPTH(1-84) (Natpara®) – as hormone replacement therapy to directly and physiologically address the unmet need in the treatment of hypoparathyroidism. Natpara is an exact, full-length 84-amino acid replica of human PTH that is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid technology. No animal-sourced proteins are used in the manufacturing process.

NPS submitted a Biologic License Application (BLA) on 24 October 2013 supporting approval of Natpara as a replacement for endogenous PTH with a proposed indication of long-term treatment of hypoparathyroidism. The recommended starting dose is 50 µg administered once daily (QD) by subcutaneous (SC) injection. If needed, the dose is titrated upward at 2- to 4-week intervals to 75 µg and then 100 µg, based on calcemic response. Downward titration in decrements of 25 µg to a minimum dose of 25 µg can occur at any time.

rhPTH(1-84) was initially developed for the treatment of osteoporosis in postmenopausal women at a high risk of bone fracture. A marketing authorization application was approved in the European Union (EU) on 24 April 2006 for Nycomed (now Takeda) for rhPTH(1-84) under the proprietary name of Preotact®. NPS also submitted an application to the United States (US) Food and Drug Administration (FDA) in 2005 for treatment of postmenopausal women with osteoporosis. In an approvable letter in March 2006, FDA required conduct of an additional Phase 3 study prior to approval. NPS did not pursue this route, changed its business model to focus on treatments for rare diseases, and later withdrew the osteoporosis application.

The marketing authorization for Preotact was transferred to NPS on 29 November 2013. NPS assessed the business opportunity for Preotact for the treatment of osteoporosis and decided to withdraw the authorization for commercial reasons. Nonetheless, the postmarketing osteoporosis data are informative and support the overall safety of

Natpara. Since approval for osteoporosis in the EU, the estimated postmarketing exposure is 61,091 patient years through 24 April 2013.

This Briefing Document reviews the efficacy experience with Natpara in treating hypoparathyroidism that supports the conclusion that Natpara restores PTH activity allowing for maintenance of serum calcium levels and management of hypocalcemic symptoms, reduction or elimination of calcium and vitamin D doses, and physiologic effects on calcium, phosphate, and bone metabolism. Safety experience in both the hypoparathyroidism and osteoporosis development programs and in the postmarketing experience in the EU is presented. Collectively, the efficacy and safety data for Natpara support a favorable benefit-risk for the long-term treatment of hypoparathyroidism.

1.1 Unmet Medical Need in Treatment of Hypoparathyroidism

The prevalence of hypoparathyroidism in the US is rare, but as with many rare diseases, the exact prevalence is unknown. It is estimated to affect approximately 60,000 patients (Powers et al., 2013; Clarke et al., 2011). While surgical technique has advanced to increase preservation of the parathyroid glands, hypoparathyroidism still results most commonly (70-80% of cases) as a postoperative sequela of thyroid, parathyroid, or other neck surgery (Rubin et al., 2010; Sikjaer et al., 2011; Bilezikian et al., 2011).

Hypoparathyroidism is a deficiency or absence of PTH, with symptoms and metabolic findings due to loss of normal physiological PTH activity. PTH has critical physiological functions that include its central role in the tight control of serum calcium and, along with other factors (e.g., fibroblast-derived growth factor 23), phosphate concentrations. In the kidney, PTH stimulates renal reabsorption of calcium and promotes phosphate excretion. PTH enhances the conversion of 25-hydroxyvitamin D (25[OH]D) to $1,25(OH)_2D$. PTH also maintains normal bone mineral activity and homeostasis (Shoback, 2008).

The presence of low-normal bone turnover markers (e.g., bone-specific alkaline phosphatase [BSAP], procollagen type 1 amino-terminal propeptide [P1NP], osteocalcin [OC], carboxy-terminal telopeptide of type I collagen [s-CTx]) reflects the low level of bone metabolism and is a hallmark of the disease (Bilezikian et al., 2011).

Hypoparathyroidism is characterized by inappropriately low circulating PTH levels in association with hypocalcemia and hyperphosphatemia, as well as hypercalciuria and hypophosphaturia. Classic symptoms are multi-faceted and are primarily related to neuromuscular irritability (e.g., asthenia, paresthesias, and tetany) as a result of hypocalcemia. Laryngospasm and bronchospasm may also indicate hypocalcemia. The cardiovascular manifestations of hypocalcemia may include congestive heart failure and arrhythmias. Neurological manifestations of hypocalcemia include symptoms such as difficulty in concentrating (“brain fog”), effects on mood and ideation, insomnia, fatigue, and seizures (Behaghel and Donal, 2011, Bilezikian et al., 2011, Arlt et al., 2002).

The goals of therapy are to maintain serum calcium, minimize hypocalcemia and the associated symptoms while avoiding complications of treating hypoparathyroidism with oral calcium and active vitamin D. Management of hypoparathyroidism is currently limited to pharmacological doses of oral calcium and active vitamin D that only address

the serum calcium concentration (Bilezikian et al., 2011; De Sanctis et al., 2012; Shoback, 2008). While there are no formal guidelines, the general approach is summarized below:

- Alleviate hypocalcemia and related symptoms – target serum calcium in low-normal range of approximately 8.0 to 8.5 mg/dL (2.00 to 2.12 mmol/L)
- lower hyperphosphatemia – target serum phosphorus in the high-normal range of 3.5 to 4.5 mg/dL (1.13 to 1.45 mmol/L)
- avoid hypercalciuria – maintain 24-hour urine calcium excretion < 300 mg/day
- maintain calcium-phosphate product < 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)

Oral calcium is typically initiated or adjusted when serum calcium drops below 7.5 mg/dL or in symptomatic patients (De Sanctis et al., 2012).

Pharmacological doses of oral calcium and active vitamin D can manage serum calcium levels and the symptoms of hypocalcemia in many patients. However, the additional effects of deficient or absent PTH are not addressed, including hypercalciuria, hyperphosphatemia, and an inability of bone to contribute to mineral metabolism. Most patients report diminished quality of life regardless of management with oral calcium and active vitamin D (Shoback, 2008).

Despite having serum calcium in the therapeutic range with oral calcium and vitamin D treatment, disordered bone metabolism is profound in the face of chronic PTH deficiency (Rubin et al., 2008). In this regard, chronic PTH deficiency leads to a low turnover state (decreased bone formation and resorption) and increased bone mass that would have otherwise been replaced during remodeling. Bone biopsy and high resolution imaging show pathological bone changes in both cancellous and cortical bone.

Chronic use of pharmacological doses of calcium and active vitamin D can be associated with morbidity on the kidney, brain, and other soft tissues due to calcification in these target tissues (Aggarwal et al., 2013). In the absence of PTH, high concentrations of serum calcium can lead to hypercalciuria and ultimately renal impairment (Shoback, 2008).

Basal ganglia calcification is common over an extended time with hypoparathyroidism. In a study of 145 hypoparathyroidism patients seen at a single endocrine clinic between 1998-2010, Goswami et al. noted basal ganglia calcification on computed tomography (CT) of the brain in 74% of patients and correlated with the duration of hypocalcemia, calcification of the choroid plexus, cataracts, and increased risk of seizure (Goswami et al., 2012). The progression of basal ganglia calcification was related to calcium/phosphorus ratio. For every 1% increase in this ratio, the odds of progression decreased by 5% (Odds ratio [OR]: 0·95, 95% CI: 0·93– 0·99, p<0·001). Treatment with calcium and active vitamin D in the absence of PTH leads to reduced renal phosphate excretion, which leads to hyperphosphatemia and an elevated calcium-phosphate product, increasing the risk of calcifications.

The multiple abnormalities in physiological processes that occur in the absence of PTH are not addressed by oral calcium and active vitamin D. As an exact full-length 84 amino acid replica of endogenous PTH, Natpara therapy is a logical, physiologic replacement strategy to fulfill the current unmet medical need in the treatment of hypoparathyroidism. Natpara exhibits all the physiological effects of PTH. Calcium, phosphate, and vitamin D metabolism may normalize, thereby stabilizing both serum calcium and phosphate concentrations within the normal ranges. In addition, treatment with Natpara can help normalize renal calcium and phosphate handling, activate vitamin D, and restore normal bone turnover.

1.2 Natpara Pharmacological Characteristics

The Natpara development program included evaluation of the pharmacokinetics and pharmacodynamics in hypoparathyroidism patients. The results characterize the pharmacokinetics, demonstrate physiologic effects on calcium and phosphate, and support a once-a-day dosing regimen for the treatment of hypoparathyroidism.

Following single SC injections of Natpara at 50 µg or 100 µg in subjects with hypoparathyroidism, peak plasma concentrations (mean T_{max}) of PTH(1-84) occurred within 5 to 30 minutes followed by a second smaller peak at 1 to 2 hours. The plasma area under the curve (AUC) increased in a dose proportional manner from 50 µg to 100 µg. The apparent terminal half-life ($t_{1/2}$) was 3.0 and 2.8 hours for the 50 and 100 µg dose, respectively. The plasma concentration data from the long-term studies in subjects with hypoparathyroidism showed that there is no accumulation of rhPTH(1-84) in the circulation and no apparent change in the pharmacokinetics of rhPTH(1-84) after up to 15 months of daily therapy.

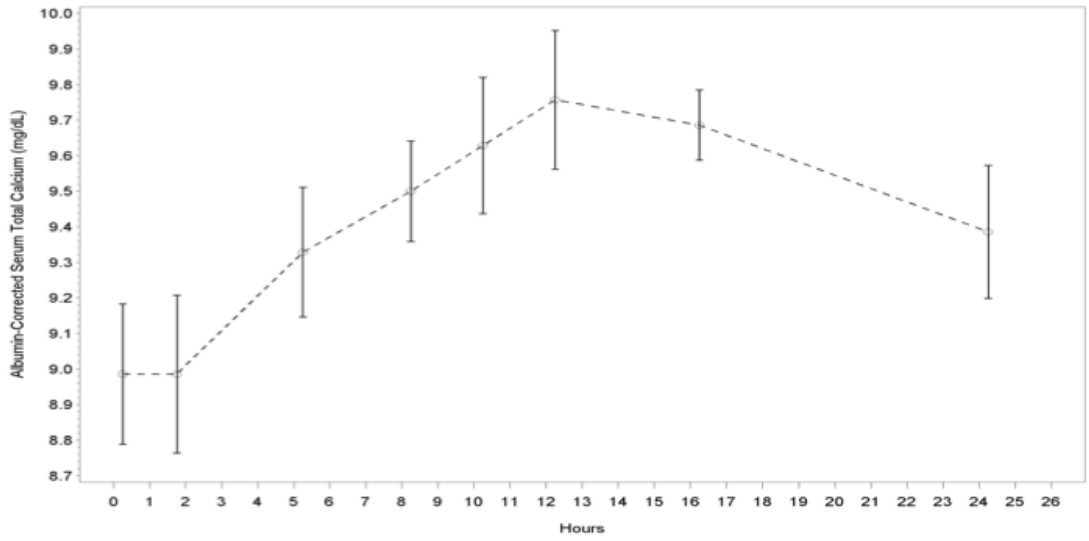
Clearance of rhPTH(1-84) is primarily hepatic with a lesser role played by the kidneys. The mean C_{max} of PTH following SC administration of a single 100 µg Natpara in subjects with mild-to-moderate renal impairment (creatinine clearance [CrCl] 30 to 80 mL/min) was approximately 22% higher than that observed in subjects with normal renal function (CrCl > 80 mL/min). No dose adjustment is necessary in patients with mild to moderate renal impairment (CrCl 30 to 80 mL/min).

Subjects with moderate hepatic dysfunction (Grade B: total score of 7 to 9 on the Child-Pugh Scale) had a 20% higher C_{max} and AUC compared to subjects with normal hepatic function. No dosage adjustments are needed for patients with moderate hepatic dysfunction.

Treatment with Natpara increases serum total calcium concentrations and decreases serum phosphate concentrations in subjects with hypoparathyroidism. In an escalating, single-dose pharmacodynamics study in 7 subjects with hypoparathyroidism (C09-002), Natpara increased serum total calcium concentrations in a dose-related manner, with maximum mean increase observed at approximately 12 hours and mean concentration sustained over baseline for more than 24 hours after administration (Figure 1). The maximum mean increases of serum calcium were approximately 0.5 mg/dL and 0.7 mg/dL with the 50 µg and 100 µg doses, respectively. One dose of Natpara provided

an appropriate 24-hour calcemic response in hypoparathyroidism patients. Baseline serum phosphate levels began at close to the upper limit of the reference range and decreased by an average of 1.5 mg/dL to near the lower quartile of the normal range by 5 hours with both the 50 and 100 µg doses of Natpara. Serum phosphate had not returned to the elevated baseline levels by 24 hours with either dose.

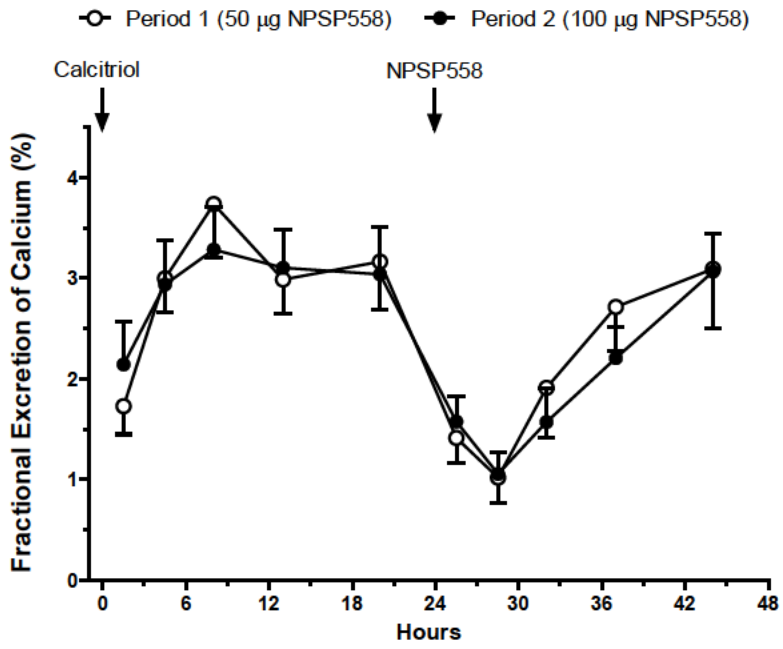
Figure 1. Mean (±SE) Albumin-corrected Serum Total Calcium



SE = standard error
Number of subjects = 7

Also consistent with the physiologic effects of PTH, urinary calcium excretion decreased by 65 to 68% at 3 to 6 hours following administration of both doses of Natpara, before increasing to predose levels in the 16- to 24-hour sample (Figure 2).

Figure 2. Mean (±SE) Urinary Fractional Excretion of Calcium Following Natpara Administration



NPSP558 = Natpara; SE = standard error
Note: Values shown are at the middle of each urine collection interval
Period 1: N = 7 (0 - 24 hours); N = 6 (24 - 48 hours); Period 2: N = 7 (0 - 48 hours).

Treatment with Natpara reduced total 24-hour urine calcium excretion by 13% and 23% following dosing with 50 µg and 100 µg, respectively (Table 1).

Table 1. Total Urinary Excretion of Calcium Over 24 Hours Following Administration of Calcitriol and Natpara

	Calcitriol 0.5-0.75 µg	Natpara 50 µg	Calcitriol 0.5-0.75 µg	Natpara 100 µg
	Day -1	Day 1	Day -1	Day 1
	(N = 7)	(N = 6)	(N = 7)	(N = 7)
Mean Calciuria mg (SD)	380 (121)	330 (165)	373 (163)	286 (131)

N = total number of subjects; SD = standard deviation

Baseline phosphate excretion increased 2.6- and 3.3-fold following administration of the 50 µg and 100 µg doses of Natpara, respectively, at 3 to 6 hours, and returned to baseline levels in the 16- to 24-hour sample.

Overall, the clinical pharmacology program showed that Natpara produced the effects expected for PTH. The data also indicates that a single SC dose of Natpara restores relatively normal calcium and phosphate metabolism lasting 24 hours in subjects with hypoparathyroidism, supporting a QD dosing regimen for the treatment of subjects with hypoparathyroidism. These pharmacokinetic and pharmacodynamic data support once daily dosing with Natpara, which is convenient and practical for patients as well as safe and effective for most patients with hypoparathyroidism.

1.3 Overview of Clinical Development Program in Hypoparathyroidism

The clinical development program of Natpara for hypoparathyroidism includes 12 clinical pharmacology studies, and 4 clinical studies in hypoparathyroidism.

There are also two published investigator-initiated trials (IIT), one conducted by Dr. John P. Bilezikian and one by Dr. Leif Mosekilde. These studies were conducted external to NPS; the findings have not been verified by NPS.

For the Mosekilde IIT, it is worthwhile to note that on the last day of study drug injection, subjects were offered participation in an NPS-sponsored 24-hour pharmacokinetic/pharmacodynamic study, the results of which were published (Sikjaer et al., 2012) and included in the Natpara BLA application.

More detailed explanation of each study in the hypoparathyroidism program is described following Table 2.

Table 2. Summary of Efficacy and Safety Studies in Subjects with Hypoparathyroidism

Study Number	Study Design	Natpara Dose[a]	Number of Subjects	Duration of Treatment[b]
CL1-11-040 (REPLACE)	R, DB, PC	50, 75, and 100 µg (flexible doses) or placebo	Natpara[c], 84; Placebo[c], 40	24 weeks
PAR-C10-007 (RELAY)	R, DB	25 or 50 µg (fixed doses)	42[c]	8 weeks
PAR-C10-008 (RACE)	OL	25, 50, 75, and 100 µg (flexible doses)	49[c]	52 weeks + extension **ONGOING**
PAR-C10-009 (REPEAT)	OL	50, 75, and 100 µg (flexible doses)	24	24 weeks

DB = double-blind; OL = open-label; PC = placebo-control; R = randomized

a. All doses of Natpara in the studies were a daily SC injection.

b. Exposure data summarized in Table 28.

c. A problem at 1 study site led to the necessity to exclude all data from 10 subjects enrolled at that site for REPLACE, 5 subjects enrolled in RELAY, and 4 subjects enrolled in RACE.

Study CL1-11-040 (referred to as REPLACE) was the largest, randomized, placebo-controlled clinical study ever conducted in a hypoparathyroidism population and was the pivotal study designed to demonstrate that Natpara is effective in maintaining serum calcium levels and enabling significant decreases in active vitamin D and oral calcium. REPLACE also established the Natpara dose and dose titration. The study also evaluated the physiologic effects of PTH replacement on serum calcium, serum phosphate, urinary calcium excretion, and bone turnover markers (BTM).

A total of 134 subjects were randomized into REPLACE, 90 to Natpara and 44 to placebo. A problem at 1 study site led to the necessity to exclude all data from 10 subjects enrolled at that site. Therefore, the remainder of the Briefing Document presents data on 84 Natpara and 40 placebo subjects in REPLACE. Of note, the REPLACE efficacy and safety results based on the analyses reported herein (i.e., excluding subjects at this site) are highly consistent with the results from analyses conducted in a data set that included all subjects.

Study PAR-C10-008 (referred to as RACE) is an ongoing, long-term (12 months plus extension), open-label study of Natpara for the treatment of adult subjects with hypoparathyroidism. A total of 53 subjects enrolled in RACE. The site excluded from the REPLACE study also participated in RACE, which led to the exclusion of data from 4 subjects who were enrolled at that site. Therefore, data is presented on 49 Natpara subjects in this study. RACE provides supportive safety and efficacy experience during long-term treatment.

The hypoparathyroidism clinical program includes an injection pen device for delivery of Natpara as a daily SC injection. The device, the Natpara® Q-Cliq™, is intended to be marketed as an integral component of the product (Figure 9)

1.4 Study Design and Efficacy Findings in REPLACE

REPLACE was a multinational (US, Canada, Western Europe, and Hungary), randomized, double-blind, placebo-controlled Phase 3 study in adult subjects (≥18 years old) with hypoparathyroidism. The study was designed to show that Natpara is effective in maintaining serum calcium levels in the setting of reduced use of oral calcium and vitamin D. The study also evaluated symptoms of hypoparathyroidism defined by adverse events (AEs) and quality of life (QoL), as well as the physiologic effects of Natpara on hypercalciuria, hyperphosphatemia, and BTM and bone mineral density (BMD). The study consisted of a 2- to 16-week optimization period for all subjects during which oral calcium and active vitamin D therapies were optimized to achieve a clinically-acceptable, stable, total albumin-corrected serum calcium (ACSC) concentration.

Eligible subjects completing the optimization period were randomized (2:1) to QD treatment with either SC Natpara or SC matching placebo. The 24-week treatment period consisted of a 12-week titration period, during which titration of study drug (as described below) and protocol-guided reduction in active vitamin D and oral calcium occurred, and a 12-week maintenance period. Efficacy was assessed at the end of treatment (EOT).

End of Treatment is defined as the last visit on treatment. Upon discontinuation of study drug, subjects entered a 4-week post-treatment follow-up period.

On Day 1 of the treatment period, all subjects received Natpara at 50 µg QD or matching placebo and had their active vitamin D dose reduced by 50%. Staged, protocol-directed changes in oral calcium and active vitamin D followed the titration of study drug dose, with doses of calcium and active vitamin D decreased if serum calcium concentration was above 9 mg/dL and increased if serum calcium was below 8 mg/dL.

Based on serum calcium levels, Natpara was up-titrated to 75 µg or matching placebo after 2 to 3 weeks of study drug dosing, and then to 100 µg or matching placebo 2 to 3 weeks later, if subjects had not achieved independence from active vitamin D and reduced oral calcium to 500 mg/day or less. Down-titration of Natpara (in 25 µg QD decrements to not less than 50 µg QD) was permitted in the presence of hypercalcemia at any time during the study for subjects who were no longer taking calcium/active vitamin D. If a subject's serum calcium was below 8 mg/dL after 8 weeks of study drug dosing, the doses of oral calcium and active vitamin D were increased.

To investigate PTH replacement for hypoparathyroidism, the REPLACE trial used primary and secondary endpoints to demonstrate that Natpara could maintain serum calcium while replacing current therapy. A triple component primary efficacy endpoint was assessed at EOT. This efficacy endpoint reflects a switch or replacement methodology that maintains serum calcium concentration while reducing or avoiding the need for oral calcium and active vitamin D administration. For a subject whose study treatment was still ongoing after Week 16, the combined endpoint of 3 components (listed below) had to be met at the EOT.

The primary triple endpoint was met only if the subject achieved:

- at least a 50% reduction from the baseline oral calcium dose, **and**
- at least a 50% reduction from the baseline active vitamin D dose, **and**
- an ACSC concentration that was maintained within a range of 7.5 to 10.6 mg/dL.

REPLACE had 3 ordered secondary endpoints: percentage change in oral calcium; active vitamin D independence with ≤ 500 mg/day of oral calcium; and frequency of hypocalcemia symptoms. The first 2 secondary endpoints characterized the components of the primary endpoint. The third endpoint was an effort to understand the prespecified hypocalcemia symptoms among patients treated to optimal serum calcium targets (and therefore minimized symptoms); the targeted serum calcium levels reflect "best" treatment of hypocalcemia as recommended in the current literature.

A total of 28 sites randomized 124 subjects (Figure 18). Of the 84 subjects randomized to Natpara, 78 completed the treatment period and 79 completed the 4-week follow-up period (i.e., completed the study). Of the 40 subjects randomized to placebo, 33 completed the treatment period and 32 completed the 4-week follow-up period.

The treatment groups were well balanced at baseline based on demographics, clinical disease characteristics, and geographic region of enrollment (52% North America, 48% Western Europe/Hungary). Overall the Intent-to-Treat (ITT) population was predominantly female (79.0%), with a mean age of 47.3 (± 12.70) years. The mean duration of hypoparathyroidism was 11.6 (± 8.12) years and 14.6 (± 11.16) years in the placebo and Natpara groups, respectively. Hypoparathyroidism was a post-surgical sequela of thyroidectomy for 65.5% of subjects in the Natpara group and 70.0% of subjects in the placebo group. In general, all subjects had baseline BMD and Z-scores that indicated a high BMD reflecting low bone turnover. Baseline mean 24-hour urinary calcium excretion was elevated but similar in the 2 treatment groups (361 and 339 mg/24 hr in the Natpara and placebo groups, respectively).

Primary Efficacy Endpoint

A significant treatment effect was observed with Natpara based on the primary efficacy endpoint (Table 3). A total of 46 of 84 subjects (54.8%) in the Natpara group and 1 of 40 subjects (2.5%) in the placebo group achieved the primary endpoint at the EOT. The treatment difference was 52.3% (95% CI for the treatment difference: 40.6% to 64.0%, $p < 0.001$), showing superiority of Natpara.

Table 3. Analysis of Primary Endpoint at End of Treatment Based on Investigator-prescribed Data (Primary Endpoint) – REPLACE

	Placebo (N= 40)		Natpara (N= 84)		Treatment Difference	
Status	**n (%)**	**(95% CI)[a]**	**n (%)**	**(95% CI)[a]**	**(95% CI)[b]**	**p-value[c]**
Met endpoint	1 (2.5)	(0.1, 13.2)	46 (54.8)	(43.5, 65.7)	52.3 (40.6, 64.0)	< 0.001
Did not meet endpoint	39 (97.5)		38 (45.2)			

CI = confidence interval; N = total number of subjects, n = number of subjects in category indicated
Note: Percentages are based on the number of subjects in each treatment arm.
a. Based on exact 95% CI.
b. Treatment difference is calculated as percentage of subjects meeting the primary endpoint in the Natpara group minus the percentage of subjects meeting the primary endpoint in the placebo group; the 2-sided asymptotic 95% CI is based on normal approximation.
c. Based on Fisher's Exact test.

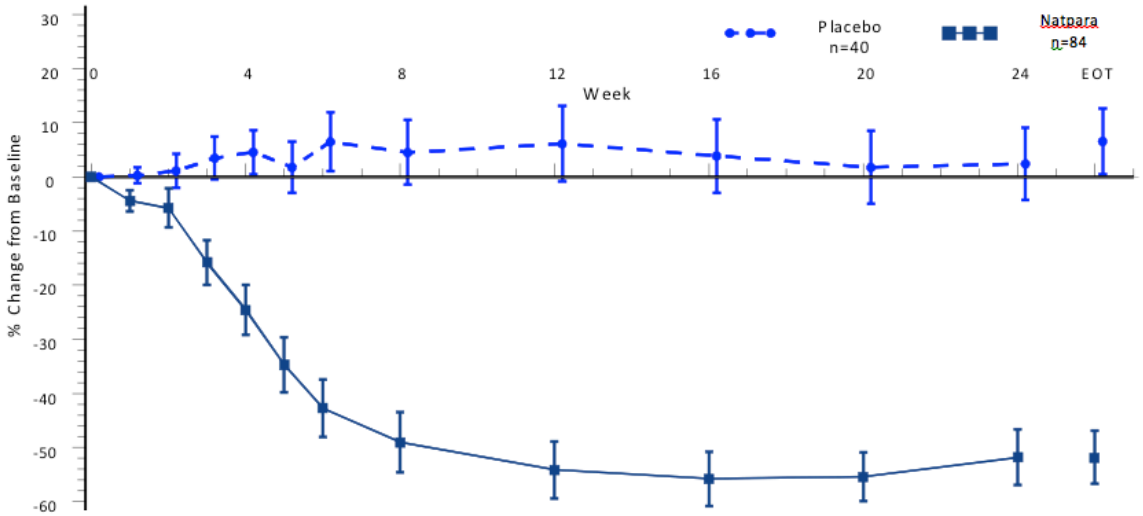
Secondary Efficacy Endpoints

REPLACE had 3 ordered secondary endpoints:

1) percentage change in oral calcium;
2) active vitamin D independence with ≤ 500 mg/day of oral calcium;
3) frequency of hypocalcemia symptoms.

At Week 24 of treatment, there was a substantial mean percentage decrease from baseline of 51.8% [± 45.7%] in calcium dose in the Natpara treatment group and a 2.4% increase in the placebo group [± 38.4%] with the difference between groups reaching significance ($p < 0.001$) (Figure 3). Mean actual and percentage changes (reductions) from baseline in investigator-prescribed calcium doses were also significantly greater in the Natpara group from Week 3 through Week 24 and at EOT ($p \leq 0.003$). Figure 20 (later in the Briefing Document) shows the reductions made to daily oral calcium dose over the course of the study.

Figure 3. Mean (±SE) of Percent Change from Baseline in Oral Calcium Dose Based on Investigator-prescribed Data –REPLACE



EOT = end of treatment (last observation during the treatment period; n = number; SE = standard error

AT EOT, 35 of 84 subjects (41.7%) treated with Natpara were independent of vitamin D treatment and were receiving no more than 500 mg of calcium based on investigator-prescribed data. In contrast, only 1 of 40 subjects (2.5%) in the placebo group achieved this endpoint at EOT. The difference between groups was clinically substantial and reached statistical significance (OR = 27.8; 95% CI: 3.7 to 212.5; $p < 0.001$). Figure 21 (later in the Briefing Document) shows the reductions made to daily oral active vitamin D dose over the course of the study.

During Week 16 to 24, 29 of 84 subject (34.5%) treated with Natpara exhibited 1 or more symptoms of hypocalcemia (defined in Section 4.1.2.2) compared to 15 of 40 subjects (37.5%) in the placebo group with the difference between groups failing to reach significance (OR = 0.879; 95% CI: 0.4 to 1.9; $p = 0.747$).

Prespecified Exploratory Endpoints

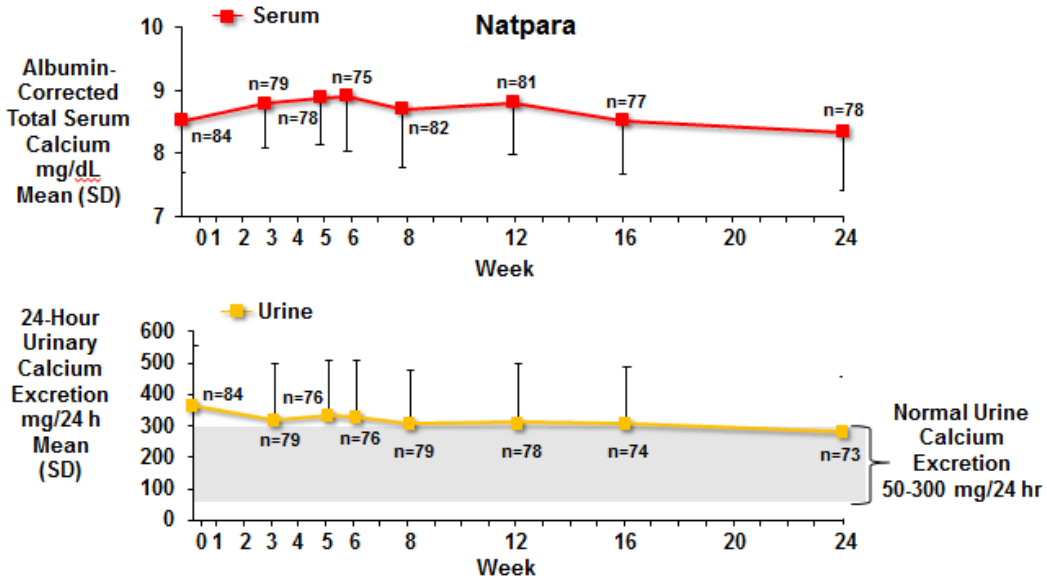
The exploratory endpoints (i.e., urinary calcium, calcium-phosphate product, bone effects, general quality of life) were prespecified and evaluated the physiologic effects of

PTH hormone replacement. At screening, mean 24-hour urinary calcium excretion was 283 mg/24 hr. After optimization, the mean 24-hour urinary calcium excretion at baseline was similarly elevated (above 300 mg/24 hr) between groups: 361 mg/24 hr in the Natpara group and 339 mg/24hr in the placebo group.

After the introduction of study drug and reduction in oral active vitamin D and calcium, the Natpara group experienced an increase in mean albumin-corrected total serum calcium (Figure 4), whereas after reduction in oral calcium and active vitamin D, the placebo group experienced a decrease in mean albumin-corrected total serum calcium (Figure 5). Over the course of the study, mean serum calcium concentration remained in the target range of 8.0 to 9.0 mg/dL in the Natpara group, while mean 24-hour urine calcium excretion decreased into the normal reference range (mean ± standard deviation [SD], 361.1 ± 193.9 mg/24 hr at baseline and 276.9 ± 177.9 mg/24 hr at Week 24) among subjects who completed treatment).

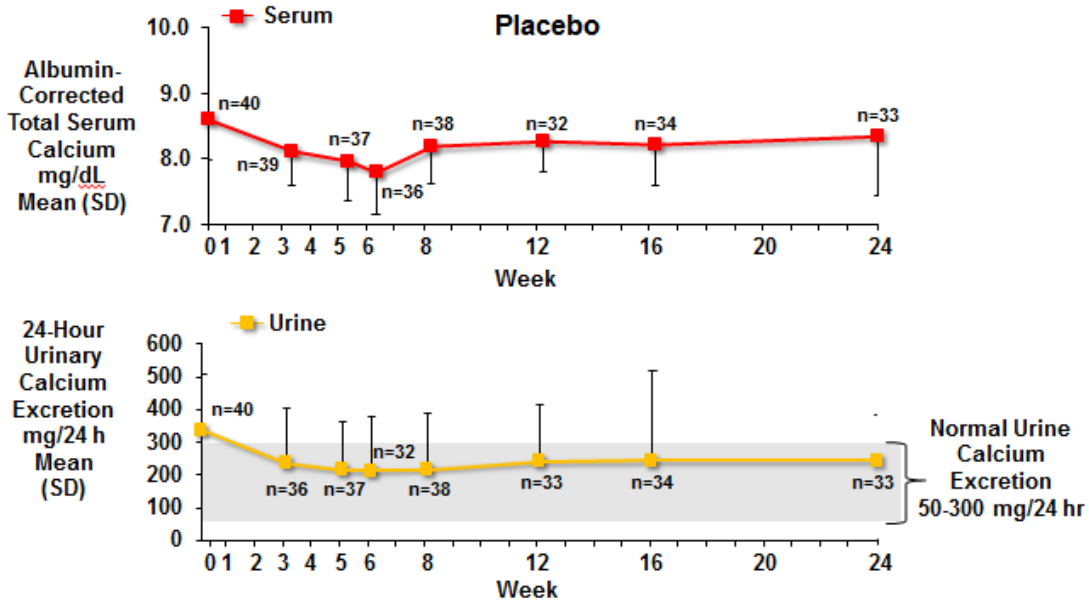
In the placebo group, mean urinary calcium excretion decreased over the first 6 weeks of REPLACE as a consequence of a mean decrease in serum calcium concentration, corresponding to withdrawal of oral active vitamin D and calcium during that time period. Increased usage of oral calcium and active vitamin D after Week 6 led to mean increases in both serum calcium concentration and urinary calcium excretion (Figure 5). These findings support the need for PTH to maintain the balance of serum and urinary calcium homeostasis.

Figure 4. Mean (± SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion – Natpara –REPLACE



SD = standard deviation
Note: Serum calcium target range: 8.0 to 9.0 mg/dL; Normal serum calcium range: 8.4 to 10.6 mg/dL
Note: Normal urine calcium excretion: 50-300 mg/24 hr

Figure 5. Mean (±SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion – Placebo –REPLACE



ITT = Intent-to-Treat; n = number; SD = standard deviation
Note: Normal urine calcium excretion is 50-300 mg/24 hr.

Shift changes from baseline in 24-hour urine calcium are displayed in Table 7 in Section 1.6, Natpara Safety Experience, of this Briefing Document.

Screening and baseline mean concentrations of serum phosphate were above the upper limit of the reference range in both treatment groups. Among subjects who completed treatment, serum phosphate levels were significantly decreased from baseline to Week 24 ($p < 0.001$) from 4.49 (± 0.66) mg/dL to 4.03 (± 0.67) mg/dL in the Natpara group and remained unchanged in the placebo group (4.53 [± 0.66] to 4.53 [±0.52] mg/dL), showing the reduction of hyperphosphatemia with PTH treatment.

Bone turnover markers were low-normal at baseline in both the Natpara and placebo treatment groups, consistent with long-term hypoparathyroidism. All BTMs (including markers of bone formation, i.e., bone-specific alkaline phosphatase [BSAP], procollagen type 1 amino-terminal propeptide [P1NP], and osteocalcin; and marker of bone resorption, i.e., carboxy-terminal telopeptide of type I collagen [s-CTx]) rapidly increased from baseline and continued to increase over the course of the study in the Natpara group. There were no changes in the placebo group with the difference between groups for all markers reaching statistical significance ($p < 0.001$ for all markers at Week 24).

Bone mineral density was measured by dual energy x-ray absorptiometry (DXA). At baseline, Z-scores (a comparison of BMD with that of an average person of the same age, sex, and ethnicity), generally indicated a high rate of mineralization with 26.9% to 64.9%

of subjects having Z-scores > 1 in each of the 7 locations scanned. At Week 24, there was a decrease towards normal in Z-scores in the Natpara group at all scan locations compared to a worsening of Z-scores in the placebo group. The changes in direct BMD measurements mirrored those of the Z-scores.

The superiority of Natpara on the primary efficacy endpoint noted above shows that Natpara treatment is able to maintain serum calcium levels while significantly reducing oral calcium and vitamin D requirements. These effects were not seen in the placebo group. Two of the 3 secondary endpoints showed statistically better results compared to placebo. The other secondary endpoint failed to show superiority to optimized current calcium therapy in reducing symptoms of hypocalcemia. Additionally, the exploratory endpoints demonstrate the underlying physiologic benefits of PTH to reduce hypercalciuria, reduce hyperphosphatemia and increase BTMs. The primary endpoint, supported by the secondary and exploratory endpoints, provides a constellation of positive evidence that demonstrate the effectiveness of Natpara as hormone replacement for the treatment of hypoparathyroidism.

1.5 Study Design and Efficacy Findings in RACE

RACE complements the findings in REPLACE and evaluates longer-term treatment with Natpara in patients with hypoparathyroidism. RACE is an ongoing, open-label study in the US to determine the long-term safety and tolerability of Natpara for the treatment of adult subjects with hypoparathyroidism. The interim cutoff date for this study in support of the Natpara BLA was 25 March 2013, which provided efficacy and safety data up to 52 weeks for a majority of subjects. This data has been updated for this document to include data up to 30 September 2013 with data up to 2 years for all safety and efficacy parameters except for bone indices.

RACE also provides an opportunity to assess longer-term efficacy. To be eligible for study entry, subjects must have previously completed REPLACE (after completing the 24-week treatment period and the 4-week follow-up withdrawal period) and/or Study PAR-C10-007 (referred to as RELAY; 8 weeks of active therapy). Treatment with Natpara was not continuous for patients transitioning from the end of REPLACE and entering into RACE. A total of 49 subjects enrolled in RACE from 1 or both of the 2 previous studies.

The investigator titrated the dose of Natpara to target effect, in the range of 25 µg SC QD to 100 µg SC QD. The starting dose of Natpara was 50 µg SC QD for subjects with a total serum calcium value of ≤ 9.5 mg/dL. Subjects with a total serum calcium value of > 9.5 mg/dL had a starting dose as follows: those taking calcium (≥ 500 mg) and/or any active vitamin D had the doses of each reduced or stopped and started Natpara treatment at a dose of 50 µg SC QD. Those taking minimal or no calcium (< 500 mg) and no active vitamin D had a starting Natpara dose of 25 µg SC QD. At any time during the study, dose titration up or down was permitted in increments of 25 µg to a maximum dose of 100 µg daily and a minimum dose of 25 µg daily.

As of the interim data cutoff for RACE, 49 subjects were enrolled at 12 US sites, 47 (96%) of whom had at least 52 weeks of continuous treatment and of these, 40 had at least 104 weeks of continuous treatment, showing good persistence on Natpara treatment. The investigators initiated treatment at 50 µg QD for 46 of the 49 study subjects, at 25 µg QD for 2 subjects, and at 100 µg for 1 subject. Thirty-three of the 49 study subjects (67.3%) underwent incremental dose titration to 100 µg SC QD and remained at that dose until the time of the interim data cut-off.

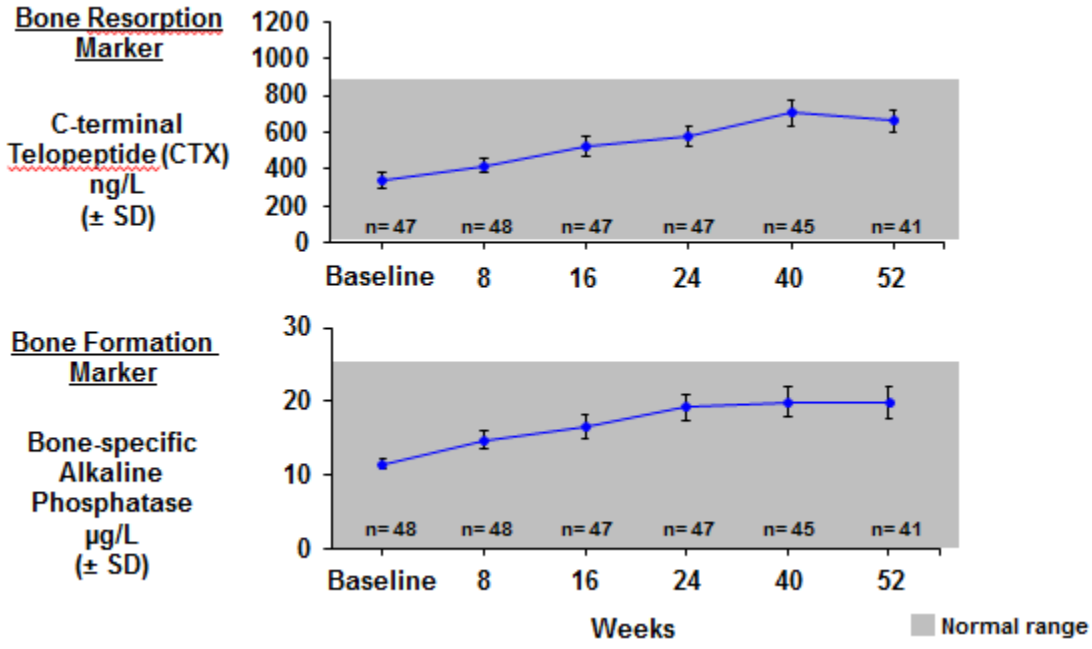
Results from the RACE study demonstrated a consistency of Natpara effect over time. At 24, 52 and 104 weeks physiological effects were maintained, including calcium-phosphate product, serum phosphate, and urinary calcium, while sustaining stable serum calcium (Table 4). Effects of Natpara on bone formation and resorption were seen by the normalization of BTMs of BSAP and CTX (Figure 6). After 104 weeks on Natpara, BMD remained unchanged from baseline, indicating maintenance of the benefit realized in the previous studies (Table 5).

Table 4. Maintenance of Physiological Effects of Natpara – RACE

Natpara Parameter, mean (SD)	Baseline (n=49)	Week 24 (n=47)	Week 52 (n=46)	Week 104 (n=39)
Albumin-corrected Serum Calcium mg/dL	8.4 (0.7)	8.4 (0.6)	8.4 (0.6)	8.3 (0.7)
Calcium-Phosphate Product mg^2/dL^2	43 (6.5)	35 (5.9)	36 (4.9)	35 (8.8)
Serum Phosphate mg/dL	4.8 (0.6)	4.0 (0.7)	4.1 (0.7)	4.2 (0.8)
24-h Urine Calcium Excretion mg/24 hours	357 (200)	-	328 (175)	281 (170)

n =total number of subjects at each time point; SD = standard deviation

Figure 6. Persistence of Effect in Bone Turnover Markers – RACE



n = number of subjects; SD = standard deviation

Note: Number of subjects at baseline refers to the baseline of RACE.

Table 5. Persistence of Effect in Bone Mineral Density – RACE

Bone Mineral Density (g/cm2) Location	Statistic	Baseline (N = 49)	Week 104 (N = 38)	Change from Baseline
Lumbar spine (L1-L4)	n	45	38	34
	Mean	1.27	1.29	0.01
	(SD)	(0.19)	(0.19)	(0.10)
Hip (total)	n	44	36	32
	Mean	1.12	1.11	-0.12
	(SD)	(0.16)	(0.16)	(0.06)
Distal one-third radius	n	45	37	33
	Mean	0.79	0.78	-0.02
	(SD)	(0.11)	(0.12)	(0.06)

N = total number of subjects; n = number of subjects at time point indicated

The findings in RACE are consistent with continued PTH activity with Natpara, supporting the long-term treatment of hypoparathyroidism.

1.6 Natpara Safety Experience

The hypoparathyroidism safety database is comprised of 361 subjects who were exposed to at least 1 dose of Natpara in the Clinical Pharmacology Studies and 121 unique subjects who were exposed to at least 1 dose of Natpara (25, 50, 75, and 100 µg SC) in the Efficacy and Safety studies in Hypoparathyroidism. The maximum exposure to Natpara exposure across the studies in hypoparathyroidism was over 3 years (162.6 weeks).

In the osteoporosis development program 2,864 subjects were treated with Natpara for a mean cumulative duration of 65.96 weeks. The postmarketing experience in osteoporosis patients is based upon an estimated 61,091 patient years (from 2006 to 2013). Osteoporosis patients, generally with normal endogenous PTH levels, received 100 µg SC doses of rhPTH(1-84), both as marketed therapy and in the clinical efficacy and safety studies.

This amount of safety data to support a rare disease indication is uncommon and helps further inform the safety profile of Natpara for the treatment of hypoparathyroidism.

The sections that follow report findings for deaths, serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and adverse events of special interest; for each category the data are presented first for the hypoparathyroidism subjects followed by the osteoporosis subjects. These data with Natpara in both hypoparathyroidism and osteoporosis are consistent with the AE profile in the literature.

Deaths in the Hypoparathyroidism and Osteoporosis Programs and Postmarketing

There were no deaths in the hypoparathyroidism development program or the randomized, controlled (6- to 24-month) trials in osteoporosis.

In the uncontrolled extension studies of osteoporosis, 7 deaths were reported, and these were associated with: myocardial infarction, aortic dissection, disseminated intravascular coagulation, ovarian cancer (1 subject each), cachexia and liver metastases (both in 1 subject), lung infection and pulmonary embolism (both in 1 subject), and pneumonia and sepsis (both in 1 subject). None of these events were unexpected in the study population and no event was reported in 2 or more patients.

In the postmarketing experience, 12 deaths were reported including: ‘acute myocardial infarction’, ‘cerebrovascular accident’, ‘pneumonia and heart failure’, ‘unresolving lower respiratory tract infection’, ‘cardiac arrest’, ‘renal and hepatic failure’, and ‘death’ (details unknown, n=6). None of these events were unexpected in the study population and no event was reported in 2 or more patients.

Serious Adverse Events in the Hypoparathyroidism and Osteoporosis Programs

In the studies in hypoparathyroidism, 10 subjects (of 121, 8.3%) experienced a total of 17 on-treatment treatment-emergent serious adverse events (TESAEs), including 1 each of back pain, cellulitis, cerebrovascular accident, chest discomfort, diarrhea, diverticulitis, dyspnea, fracture, gastroenteritis, hypercalcemia, hypocalcemia, metastatic

adenocarcinoma of the lung, radius fracture, syncope, throat tightness, ulna fracture, viral infection, and vomiting. None of these events were unexpected in the study population and the investigator considered all on-treatment TESAEs not related to study drug, with one exception (hypercalcemia).

In the osteoporosis program 7% of 2864 subjects experienced a TESAE, with no specific SAE occurring in > 0.3% of subjects. The most common TESAEs were hypercalcemia (10/2864, 0.3%), angina pectoris (7/2864, 0.2%), breast cancer (6/2864, 0.2%), and non-cardiac chest pain 6/2864, 0.2%).

Additionally, across the clinical studies of Natpara for hypoparathyroidism and osteoporosis as well as the postmarketing experience in osteoporosis, there have been no reports of osteosarcoma.

Treatment-Emergent Adverse Events in Hypoparathyroidism Studies and Osteoporosis Studies

In REPLACE, the on-treatment TEAEs reported in ≥ 5% of the Natpara-treated subjects and at a rate ≥ 2-fold greater than placebo were hypercalcemia (16/84, 19.0% vs. 1/40, 2.5%), diarrhea (10/84, 11.9% vs. 1/40, 2.5%), vomiting (10/84, 11.9% vs. 0/40, 0%), anxiety symptoms (6/84, 7.1% vs. 0/40, 0%), hypomagnesemia (6/84, 7.1% vs. 0/40, 0%), and neck pain (6/84, 6.0% vs. 1/40, 2.5%). The TEAE reported in ≥ 5% of the placebo-treated subjects and at a rate ≥ 2-fold greater than Natpara was fatigue (8/40, 20.0% vs. 8/84, 9.5%), lower respiratory tract infection (4/40, 10.0% vs. 1/84, 1.2%), and urinary tract infections (2/40, 5.0% vs 2/84, 2.4%).

In the placebo-controlled osteoporosis studies, which included 1696 Natpara-treated subjects and 1425 placebo-treated subjects, the only on-treatment TEAEs for which the incidence rate in Natpara-treated subjects exceeded the incidence rate in placebo-treated subjects by 2-fold were hypercalcemia (22.9% vs. 3.9%) and nausea (20.2% vs. 8.6%). There were no on-treatment TEAEs for which the incidence rate in placebo-treated subjects exceeded the incidence rate in Natpara-treated subjects by 2-fold in placebo-controlled osteoporosis studies.

Adverse Events of Special Interest

Hypocalcemia, hypercalcemia, and hypercalciuria were considered adverse events of special interest (AESI) in the Natpara hypoparathyroidism development program. Each of the AESIs was evaluated based on TEAE reporting and also based on laboratory test results, with or without symptoms.

An AE grouping term that included combined Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) was used to analyze the AESI. For the AESI of hypocalcemia, the PTs used were hypocalcemia and blood calcium decreased. For the AESI of hypercalcemia, the PTs used were hypercalcemia and blood calcium increased. For AESI of hypercalciuria, the PTs used were hypercalciuria and urine calcium increased. The results of this analysis for hypocalcemia and hypercalcemia in REPLACE are presented in Table 6.

Table 6. Summary of Adverse Events of Special Interest of Hypocalcemia and Hypercalcemia in REPLACE

	Placebo N = 40	Natpara N = 84
	n (%)	n (%)
Hypocalcemia:		
Optimization (before the first dose date)	3 (7.5)	7 (8.3)
Treatment (the first dose date to the last dose date)	9 (22.5)	23 (27.4)
Post-treatment period[a]	3 (9.4)	22 (27.8)
Hypercalcemia:		
Optimization (before the first dose date)	0	3 (3.6)
Treatment (the first dose date to the last dose date)	1 (2.5)	16 (19.0)
Post-treatment period[a]	3 (9.4)	2 (2.5)

N = total number of subjects in the treatment group
Note: The number of events reported do not include events ongoing from previous study periods, i.e., new events only
a. Number of subjects in the post-treatment period = Natpara, 79; Placebo, 32

In REPLACE, hypocalcemia was reported as an AESI throughout the study. No AESI of hypocalcemia reported during the on-treatment period met the regulatory definition of serious or led to discontinuation. To investigate the effect of sustained withdrawal of Natpara, on the last day of treatment baseline doses of oral calcium and active vitamin D were re-introduced while Natpara was withheld for the subsequent 4 week withdrawal period. After complete and sustained withdrawal of study drug at study end, 22 (28.0%) Natpara-treated subjects and 3 (9.0%) placebo-treated subjects experienced a new post-treatment AESI of hypocalcemia. In 2 Natpara-treated subjects and 1 placebo subject, the post-treatment hypocalcemia was considered serious, and each of these subjects required intravenous (IV) calcium gluconate. In addition, 3 Natpara-treated subjects with non-serious post-treatment AESIs of hypocalcemia required IV calcium infusion. These events occurred 2 to 8 days following treatment withdrawal. These findings demonstrate that sustained withdrawal of Natpara treatment in hypoparathyroidism subjects needs to be accompanied by reinstitution of pharmacological doses of oral calcium and vitamin D and frequent monitoring of serum calcium.

Two on-treatment events of hypocalcemia occurred during the REPLACE study which required emergency room visits. These events occurred on Study Days 71 and 133. The subjects were treated with IV magnesium sulfate and IV calcium chloride on these days, respectively.

Accidental missed doses were not associated with severe cases of hypocalcemia and therefore pose minimal risk to patients. During the on-treatment period with Natpara, 23 subjects missed at least 1 dose of Natpara on 36 occasions, according to their

e-diaries. These missed doses of Natpara were associated with mild to moderate symptoms of hypocalcaemia in 4 patients. No ER visits were necessary and all events resolved. The risk of hypocalcemia when treatment with Natpara is interrupted is identified and described in the Risk Management Plan to alert prescribing physicians of this risk.

An AESI of hypercalcemia was reported most often during the initial titration period of REPLACE when most adjustments in study drug and oral calcium/active vitamin D occurred. One subject in the Natpara group and none in the placebo group had an AESI of hypercalcemia that met the regulatory definition of serious; no subject had an AESI of hypercalcemia that led to discontinuation. After complete and sustained withdrawal of study drug, 3 placebo subjects (7.5%) and 2 Natpara-treated subjects (2.4%) experienced a post-treatment AESI of hypercalcemia.

With regard to hypercalciuria, 6 subjects (7.1%) who were eventually randomized to Natpara and 2 subjects (5.0%) who were eventually randomized to placebo experienced at least 1 AESI of hypercalciuria during the optimization period (pre-randomization). Eight Natpara subjects (9.5%) and 3 placebo subjects (7.5%) experienced at least 1 AESI of hypercalciuria during Weeks 1 through 12 (titration period), as did 8 Natpara-treated subjects (9.5%) and 2 placebo subjects (5.0%) during the stable period. No AESI of hypercalciuria reported during the on-treatment period met the regulatory definition of serious or led to discontinuation. A post-treatment AESI of hypercalciuria was reported for 5 (6.0%) and 2 (5.0%) of subjects in the Natpara and placebo groups, respectively.

The 24-hour urine calcium results at baseline and at Week 24 provide further information about hypercalciuria over time. For the subjects with urine calcium data available at both baseline and Week 24, approximately half of subjects had 24-hour urine calcium excretion > 300 mg/24 hr at baseline (57% [42/74] and 48% [16/33] of subjects in the Natpara and placebo groups, respectively). At Week 24, a lower percentage of subjects in the Natpara group (34%, 25/74) as compared to the placebo group (39%, 13/33) had 24-hour urine calcium excretion > 300 mg/24 hr. Additionally, more patients on Natpara reduced urinary calcium from high to normal and fewer Natpara-treated patients shifted from normal to high, compared with placebo, supporting the role of PTH in reducing the rate of hypercalciuria (Table 7).

Table 7. Shift in 24-hour Urinary Calcium from Baseline to Week 24 – Subjects Who Completed 24 Weeks of Treatment - REPLACE

Changes in 24-hour Urine Ca (mg/day) from Baseline to Week 24	Natpara N=74		Placebo N=33	
	n	%	n	%
Patients with > 300mg/day at baseline	42	57%	16	48%
Patients with > 300mg/day at Week 24	25	34%	13	39%
From > 300 to ≤ 300 (high to normal)	24	32%	8	24%
From ≤ 300 to > 300 (normal to high)	7	9%	5	15%

Ca = calcium; N= total number of subjects; n = number of subjects with available 24-hour urine calcium data at both baseline the corresponding visit week.

In the long-term study, RACE, in those subjects who completed 24 months of treatment, there were a similar percentage of subjects (61%) who had a baseline calcium excretion of > 300mg/24 hours, as in REPLACE (57%). Over time the percentage of subjects with hypercalciuria decreased to 37% at Month 24 (Table 8).

Table 8. Persistence of Effect – Reduction in Hypercalciuria – RACE

Visit for RACE Completers	Patients with Urine Ca > 300 mg/24 hours n/N	%
Baseline following REPLACE & RELAY	23/38	61%
Month 4	20/36	56%
Month 8	12/37	32%
Month 12	19/36	53%
Month 16	12/36	33%
Month 20	9/35	26%
Month 24	14/38	37%

Ca = calcium; N = total number of subjects completing Natpara treatment; n = number of subjects with hypercalciuria at timepoint shown

In these subjects the incidence of hypercalciuria typically fluctuated over time, but most subjects did not have persistent hypercalciuria, based on measurements at each of the 7 study visits (Table 9).

Table 9. Persistence of Hypercalciuria – RACE

Incidences of Hypercalciuria[a]	Number of Subjects	Percent of Subjects
≥ 4	9	22.5
≥ 5	7	17.5
≥ 6	4	10.0
≥ 7 (all visits)	4	10.0

a. Hypercalciuria is defined as a 24-hour urine calcium measurement of ≥ 300 mg/24 h
Note: The number of subjects with measurements of 24-hour urine at Month 24 = 40.

1.7 Conclusions

Hypoparathyroidism is a rare disease attributable to deficiency or absence of PTH, with symptoms and metabolic findings attributable to loss of normal physiological PTH activity. PTH has critical physiological functions that include its central role in the tight control of serum calcium and, along with other factors (e.g., fibroblast-derived growth factor 23), serum phosphate concentration. In the kidney, PTH stimulates renal reabsorption of calcium and promotes phosphate excretion. PTH enhances the conversion of 25(OH)D to $1,25(OH)_2D$. PTH also enables normal bone mineral physiology.

The current standard of treatment for hypoparathyroidism is oral calcium and active vitamin D, which are prescribed to maintain serum calcium levels and minimize symptoms of hypocalcemia. However, oral calcium and vitamin D do not address the underlying PTH deficiency, rendering patients subject to the physiologic consequences of hypercalciuria, hyperphosphatemia, and reduced bone turnover. Physiologically without PTH, any increase in serum calcium results in increased urinary calcium, which can lead to hypercalciuria. Active vitamin D increases phosphate absorption in the kidney, which in the absence of PTH results in hyperphosphatemia. The combination of raising serum calcium through supplementation with the occurrence of hyperphosphatemia, results in high calcium-phosphate product and long-term soft tissue deposition of calcium. Additionally, without the normal effects of PTH on bone, the bone structure becomes abnormal and bone mineral metabolism is impaired, hindering the ability to mobilize calcium from bone.

Over the course of this chronic disease, patients accumulate longer-term sequelae due to the absence of PTH and the complications of calcium supplementation. Thus, there is medical necessity for a treatment of hypoparathyroidism that restores PTH activity and directly addresses the underlying disease and its physiologic effects. NPS developed Natpara, an exact full-length, 84-amino acid replica of endogenous PTH, as hormone replacement therapy to address these needs.

The pharmacodynamic properties of rhPTH(1-84), a recombinant human PTH that is manufactured using a strain of *Escherichia coli* (*E. coli)* modified by recombinant DNA technology, were investigated across a number of studies. The findings confirm that Natpara produces the expected physiological responses including maintenance of serum calcium, decreased serum phosphate concentration, and reduction in hypercalciuria in hypoparathyroidism patients (Table 10). Mean serum total calcium reaches its peak concentration between 10 and 12 hours following SC injection and is sustained for more than 24 hours after administration. A daily dose of Natpara provides an appropriate 24-hour calcemic response in hypoparathyroidism patients (while decreasing the requirement for oral calcium and active vitamin D).

The REPLACE study confirmed that Natpara is superior to placebo and effective in maintaining serum calcium with reduction in oral calcium and active vitamin D doses. The primary efficacy endpoint was assessed at the end of 24 weeks of treatment (following optimization of oral calcium and active vitamin D to stabilize serum calcium levels). The primary triple endpoint was met only if a subject achieved:

- at least a 50% reduction from the baseline oral calcium dose, **and**
- at least a 50% reduction from the baseline active vitamin D dose, **and**
- an ACSC concentration that was maintained or normalized at Week 24 compared to the baseline value (≥ 7.5 mg/dL) and did not exceed the upper limit of normal (ULN).

Each component in the response definition represents an endpoint of clinical significance. The minimum 50% reduction in oral calcium and active vitamin D is substantial given the dosing levels that many patients with hypoparathyroidism must maintain in order to control serum calcium levels.

Subjects assigned to Natpara had a significant treatment effect when compared to subjects assigned to placebo. Overall, 54.8% in the Natpara group met the endpoint compared to 2.5% in the placebo group ($p < 0.001$). Results of secondary (first 2 of 3) and prespecified exploratory endpoints confirmed Natpara efficacy in REPLACE.

The REPLACE design was conservative in assessing whether patients met the primary endpoint by requiring an early response on study without the opportunity for a more prolonged titration effort as could occur in standard medical practice. Since the protocol did not permit study drug to be dose titrated after 8 weeks and the majority of changes to calcium or active vitamin D were to be completed by 12 weeks, investigators did not have much time to titrate to effect. In clinical practice, clinicians will titrate Natpara on an individualized basis, while calcium and active vitamin D are being reduced without the necessity to complete the titration and reduction in oral calcium and vitamin D within a defined 8-week period.

Long-term experience with Natpara was examined in the RACE study (1 year; plus ongoing extension) affirming that the PTH activity of Natpara continues with long-term treatment.

Overall, the Natpara development program in hypoparathyroidism established that Natpara produces PTH activity both in the short and long term. Table 10 summarizes the advantages that restoring normal PTH activity provides over current treatment in the management of patients with hypoparathyroidism.

Table 10. Treatment Effects in Hypoparathyroidism

Action in Hypoparathyroidism	Calcium and/or Active Vitamin D	Natpara
Increase serum calcium concentrations	Yes	Yes
Promote renal calcium reabsorption	No	Yes
Decrease serum phosphate	No (could worsen)	Yes
Decrease calcium-phosphate product	No (could worsen)	Yes
$1,25(OH)_2$ vitamin D production	No, only provided orally	Yes
Normalize bone turnover	No	Yes

The overall safety experience in the hypoparathyroidism and osteoporosis clinical development programs as well as in significant osteoporosis postmarketing experience supports the safety of Natpara. Events of hypocalcemia, hypercalcemia, and hypercalciuria were observed with Natpara treatment; hypercalcemia and hypercalciuria were noted primarily during Natpara titration while oral calcium and active vitamin D were being adjusted. Incidences of hypercalciuria during long-term treatment with Natpara did not show a pattern of persistence, but occurred sporadically throughout the time on treatment. Hypocalcemia occurred throughout the clinical studies, however, most occurrences were mild or moderate and no event led to discontinuation. These events are manageable by measuring calcium during the titration phase or in the setting of complete, sustained withdrawal by adjusting Natpara dosing and/or oral calcium and active vitamin D supplementation, respectively. Education of patients about these risks will be part of NPS' Risk Management Plan (RMP) which includes a network of nurses who will visit patients' homes at least twice, at the initiation of Natpara treatment and 15 days later. No unique findings were reported in the osteoporosis development program or postmarketing experience, further reinforcing the safety profile of Natpara.

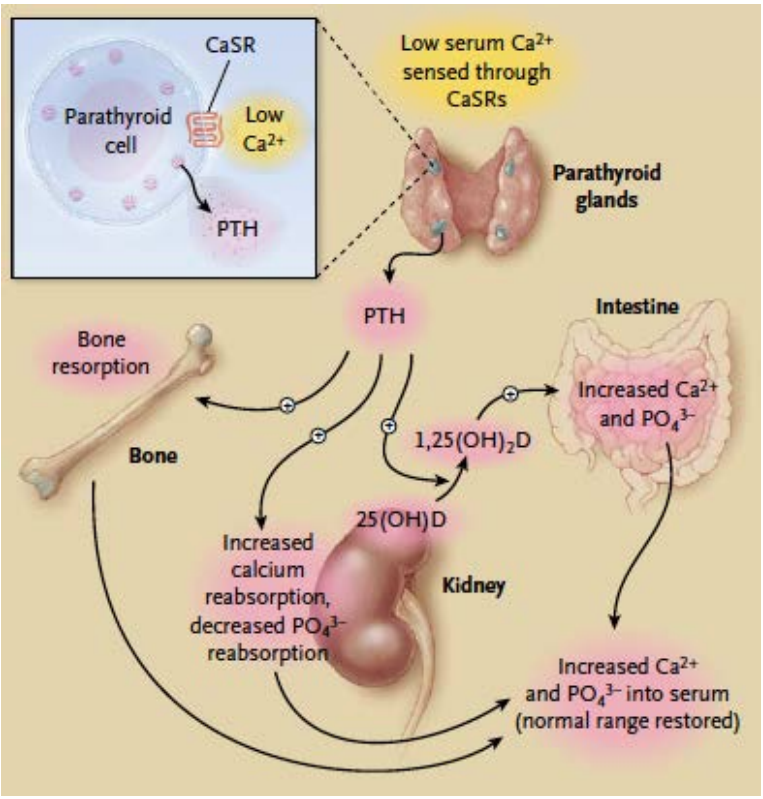
In summary, Natpara addresses an important unmet medical need in hypoparathyroidism for a treatment to restore the activity of endogenous PTH. Natpara is a well-tolerated, hormone replacement treatment for hypoparathyroidism patients that maintains serum calcium, reduces or eliminates the need for oral calcium and active vitamin D, and provides positive physiologic effects on rates of hypercalciuria, reduction of hyperphosphatemia and more normalized BTMs and BMD. The results of the development program support the approval of Natpara for the long-term treatment of patients with hypoparathyroidism.

2 UNMET MEDICAL NEED IN TREATMENT OF HYPOPARATHYROIDISM

2.1 Normal Parathyroid Physiology

Parathyroid hormone (PTH), an 84-amino acid protein, is secreted by the parathyroid glands. PTH has a variety of critical physiological functions that include its central role in modulating serum calcium and phosphate concentrations within a tightly controlled range, regulating renal calcium and phosphate excretion, activating vitamin D, and maintaining normal bone turnover (Figure 7).

Figure 7. PTH Regulation of Calcium and Phosphate Homeostasis



Source: Shoback, 2008.

Healthy subjects exhibit an endogenous circadian pattern in plasma PTH secretion, showing a late afternoon/early evening rise and fall and a broader, longer-lasting increase late evening/early morning, reaching nadir mid-morning (Fraser et al., 2004). This pattern of PTH secretion is associated with rhythms in serum calcium and biological markers of PTH's effect (e.g., at the kidney; urinary calcium/creatinine, urinary phosphate/creatinine) (el-Hajj Fuleihan et al., 1997; Jubiz et al., 1972).

The parathyroid glands are sensitive to the concentration of extracellular calcium (via the binding of calcium to extracellular calcium "sensing" receptors [CaSR] expressed on the plasma surface membrane of parathyroid cells) and adjust the synthesis and secretion of

PTH accordingly. If extracellular calcium is low, the parathyroid glands increase PTH secretion, and vice versa (Bilezikian et al., 2011).

CaSRs are widely distributed in the human body – kidney, gastrointestinal (GI) tract, bone (in osteoblasts and osteoclasts), central nervous system (in the brain: subfornical organ, hippocampus, and in glial cells), breast (normal and malignant tissue), epidermal cells, heart (in myocytes and endothelial cells of the cardiac microvasculature), and aorta – which may explain how fluctuations in serum calcium may lead to multiple, diverse symptoms (Section 2.2.4) (Magno et al., 2011).

PTH Effect on the Kidney

In the kidney, PTH increases renal tubular reabsorption of calcium and stimulates the conversion of native 25(OH) vitamin D into the active metabolite, $1,25(OH)_2$ D, or calcitriol), which facilitates the absorption of calcium and phosphate from the intestine (Nissenson and Jüppner, 2008). In the absence of PTH, patients with hypoparathyroidism have low endogenous concentrations of $1,25(OH)_2D$, one of the paramount reasons that hypoparathyroidism patients cannot properly absorb dietary calcium. High calcium load in the kidney in hypoparathyroidism can lead to adverse effects (nephrolithiasis and nephrocalcinosis, impaired renal function). PTH also has a phosphaturic effect. In hypoparathyroidism, therefore, hyperphosphatemia is commonly seen, which may facilitate extraskeletal calcifications (Sikjaer et al., 2012). A common test used to assess the effect of parathyroid gland function on the kidney is 24-hour urinary excretion of calcium; hypoparathyroidism patients often have high urinary calcium excretion.

PTH Effect on Bone

PTH maintains normal bone mineral activity and homeostasis. PTH increases the efflux of calcium from bone, both from the rapidly exchangeable pool of calcium within bone (bone holds 99% of total body calcium), and by increasing the number and activity of osteoblasts and osteoclasts, thereby increasing bone turnover (Favus and Goltzman, 2008). Markers of bone formation or bone resorption generally reflect secretory or breakdown products of bone cells (osteoblasts, osteoclasts, or osteocytes) or bone collagen as it is being formed or resorbed. They are used as indirect tools to assess bone turnover and to provide information about the metabolic status of bone in patients with hypoparathyroidism (Costa and Bilezikian, 2013).

The most frequently measured serum markers of bone resorption are:

- C-terminal cross-linking telopeptides of type I collagen (CTX)
- tartrate-resistant acid phosphatase 5b (TRAP)

Bone formation markers, products of osteoblast activity, can be assessed by the measurement of:

- bone-specific alkaline phosphatase (BSAP)
- osteocalcin (OC), and

- N-terminal cross-linking propeptides of type I procollagen (P1NP)

Bone mineral density testing and bone biopsy with histomorphometric analysis also provide useful information about the bone structure and quality.

PTH Effect on Calcium, Phosphate, and Magnesium

The net effect of increasing PTH levels is to increase serum calcium, reduce urinary calcium excretion, and increase urinary phosphate excretion (lowering serum phosphate concentrations). Parathyroid hormone may also play a role in the regulation of magnesium metabolism. PTH modulates magnesium reabsorption by increasing influx of magnesium into the distal convoluted cell. Additional humoral factors (e.g., calcitonin, vitamin D) and the CaSR also play roles in magnesium homeostasis. In a reciprocal manner, magnesium acts as a negative regulator of PTH release from the parathyroid gland in a manner similar to calcium (Vetter et al., 2002).

2.2 Overview of Hypoparathyroidism

2.2.1 Epidemiology

Hypoparathyroidism is a rare, complex endocrine deficiency that is characterized by absent or inappropriately low circulating PTH levels in association with hypocalcemia and hyperphosphatemia (Figure 7), as well as hypercalciuria and hypophosphaturia. Hypoparathyroidism is rare, and as with many rare diseases the exact prevalence is unknown. In the US, it is estimated to affect approximately 60,000 patients (Powers et al., 2013; Clarke et al., 2011).

2.2.2 Etiology

While advances have been made to preserve the parathyroid glands during thyroid surgery (e.g., microsurgical approach, parathyroid glands autotransplantation) (Testini et al., 2007), hypoparathyroidism is most often (70-80% of all hypoparathyroidism cases) a postoperative sequela of thyroid or other neck surgery (Rubin et al., 2010; Sikjaer et al., 2011; Bilezikian et al., 2011). It occurs in about 0.9% to 6.6% of patients following thyroidectomy, with the higher rates associated with more complicated interventions (Shoback, 2008; Thomusch et al., 2003; Zarnegar et al., 2003; Page et al., 2007; Puzziello et al., 2014). The second most common cause of hypoparathyroidism is damage to the parathyroid glands as a result of a local autoimmune process or as a part of an autoimmune polyendocrine syndrome (Bilezikian et al., 2011). Other causes include congenital absence of the parathyroid glands, genetic mutations, iron overload syndromes (thalassemia), copper deposition in the parathyroid gland from Wilson's disease and, very rarely, radiation damage or metastatic infiltration (Shoback, 2008; Bilezikian et al., 2011).

2.2.3 Diagnosis

The diagnosis of hypoparathyroidism is based on hypocalcemia noted on repeat testing that is associated with an absent or inappropriately low serum PTH concentration, normal serum magnesium and sufficient vitamin D. While the diagnosis is not difficult to make,

it is often not called hypoparathyroidism, but rather oversimplified as hypocalcemia (De Sanctis et al., 2012).

2.2.4 Clinical Manifestations

Classic symptoms of hypoparathyroidism are multi-faceted and are primarily related to neuromuscular irritability as a result of hypocalcemia (e.g., asthenia, paresthesia, and tetany; Table 11). Laryngospasm and bronchospasm may also indicate hypocalcemia. The cardiovascular manifestations of hypocalcemia may include congestive heart failure and arrhythmias. Neurological manifestations of hypocalcemia include symptoms such as difficulty in concentrating ("brain fog"), effects on mood and ideation, insomnia, fatigue, and seizures. Additionally, because PTH maintains normal bone mineral activity and skeletal homeostasis, disordered bone metabolism is profound in the face of chronic PTH deficiency (Rubin et al., 2008). In this regard, chronic PTH deficiency leads to a low turnover state (decreased bone formation and resorption) and increased bone mass that would have otherwise been replaced during remodeling. This increase in BMD is not necessarily a beneficial effect because the bone is typically hypermature. Bone biopsy and high resolution imaging show pathological bone changes in both cancellous and cortical bone (Bilezikian et al., 2011; Rubin and Bilezikian, 2010; Rubin et al., 2011a; Rubin et al., 2011b; Sikjaer et al., 2011; Sikjaer et al., 2012). Mendonca et al. have addressed the consequences of abnormal skeletal microstructure and macrostructure by noting the frequency of subclinical vertebral fractures (Mendonca et al., 2013). Vertebral fragility fractures are more likely to occur in patients with hypoparathyroidism despite normal or even high BMD.

In another study which used hospital discharge data and prescription data from the Danish National Patient Registry, Underbjerg et al. (2014) found no difference in the risk of any fracture in patients with post-surgical hypoparathyroidism, although there was a decrease in fractures of the proximal humerus and the upper extremities.

Table 11. Classic Symptoms and Signs of Hypoparathyroidism or its Treatment

Body System Symptom/Sign
Neuromuscular
• Asthenia
• Paresthesias (oral, perioral, and acral)
• Tetany (carpopedal and generalized)
• Bronchospasm, laryngospasm
Cardiac
• Rhythm and conduction disturbances (e.g., prolonged QT in the face of hypocalcemia, T-wave inversion)
• Palpitations
• Edema
• Cardiomyopathy
CNS
• Difficulty in concentrating ("brain fog")
• Effects on mood and ideation
• Chronic headaches
• Insomnia
• Fatigue
• Seizures
Bone
• Fractures
• Myalgia
Calcification of Tissues[a]
• Nephrocalcinosis
• Nephrolithiasis
• Basal ganglia
• Intraocular lens (cataracts)
Kidney
• End-stage kidney disease

a. As a result of oral calcium and active vitamin D.
Source: Arlt et al., 2002; Behaghel and Donal, 2011; Bilezikian et al., 2011; De Sanctis et al., 2012; Shoback, 2008; Velasco et al., 1999

Bone Fracture

Risk of fracture and other complications were reported by Mitchell et al., who reviewed the charts of 120 hypoparathyroidism patients (mean age at onset = 35 ± 21 years; mean duration of the disease = 17 ± 16 years) seen at a Boston tertiary-care hospital system between 1988 and 2009 (Mitchell et al., 2012). In this longitudinal study, the majority of patients (94%) were taking calcium and calcitriol (88%); 20% were taking a thiazide diuretic, and 6% high-dose vitamin D. Over a mean follow-up period of 7.4 years, 21 patients (18%) sustained 44 reported fractures (12 vertebral, 8 rib, 5 each ankle, digit, and arm, 4 metatarsal, 2 nose, and 1 each wrist, hip, and clavicle).

Renal Complications

Mitchell et al. reported that 41% (44/107) of adults with hypoparathyroidism had an estimated GFR < 60 mL/min/1.73 m^2 (Mitchell et al., 2012). Rates of chronic kidney disease stage 3 or higher were 2- to 17-fold greater than age-appropriate norms from the National Health and Nutrition Examination Survey 1999–2006. Two patients (1.6%) required renal transplant due to nephrocalcinosis; 1 occurred 11 years following diagnosis. Seventeen (of 54 who underwent imaging; 31%) had either renal stones or nephrocalcinosis (associated with oral calcium and/or active vitamin D, as described in Section 2.3), 5 of whom were symptomatic. In a related case-control study, Underbjerg et al. reported that patients with hypoparathyroidism had a more than 3-fold increased risk of renal complications (hazard ratio, 3.67; 95% CI: 2.41-5.59) (Underbjerg et al., 2013).

Basal Ganglia Calcification

Basal ganglia calcification is common over an extended period among patients with hypoparathyroidism. In a study of 145 hypoparathyroidism patients seen at a single endocrine clinic between 1998 and 2010, Goswami et al. noted basal ganglia calcification on computed tomography (CT) of the brain in 74% of patients. The presence of calcifications correlated with the duration of hypocalcemia, calcification of the choroid plexus, cataracts, and increased risk of seizure (Goswami et al., 2012). The progression of basal ganglia calcification was related to calcium/phosphorus ratio. For every 1% increase in this ratio, the odds of progression decreased by 5% (OR: 0·95, 95% CI: 0·93-0·99, p<0·001). Likewise, in their chart review, Mitchell et al., noted that 16 patients (of 31 with brain imaging; 52%) had basal ganglia calcification (Mitchell et al., 2012). These complications occurred despite the fact that serum calcium was maintained between 7.5 and 9.5 mg/day for the majority of the time (median 86%; IQR 67-98%), although they noted that 9.5 mg/dL is high for most patients with hypoparathyroidism.

Health Care Resource Utilization

Mitchell et al. reported that one-third of patients required at least one emergency department visit or hospital admission for complications of hypoparathyroidism, including 8 (7%) during the last year of observation and 16 (13%) during the last 2 years (Mitchell et al., 2012). Reasons for visits included symptomatic hypocalcemia (62% of visits), symptomatic hypercalcemia (12%), and other causes (26%), including renal

stones, complications of hemodialysis, and complications of intravenous (IV) calcium extravasation.

Diminished Quality of Life

Multiple studies have demonstrated that the heavy burden of disease impacts hypoparathyroidism patients' quality of life (QoL). Using the widely used and well-validated Short Form-36 (SF-36) Healthy Survey, a measure of health-related QoL covering 8 domains of physical and mental health, Cusano et al. determined that hypoparathyroidism is associated with QoL deficits even in the presence of adequate calcium and active vitamin D to maintain eucalcemia (Section 2.3) in most patients (Cusano et al., 2013a). Patients with hypoparathyroidism scored significantly lower (i.e., worse) than the normative reference range (for healthy US men and women) in all 8 domains ($p<0.05$ for all comparisons).

In line with these findings, Cho et al. recently noted that patients with hypoparathyroidism reported significantly lower mean QoL scores than a control group in each of the 8 domains measured by a modified, disease-specific SF-36 Health Survey ($p<0.001$ for all comparisons) (Cho et al., 2013). The largest difference between the groups was in the energy/fatigue domain. Other domains with similarly striking between-group differences in score included role limitations due to physical health, role limitations due to emotional problems, and general health. Of note, physicians significantly underestimated (using a subset of questions from the modified SF-36) the impact of hypoparathyroidism on patient QoL, as compared to reports from the patients living with chronic hypoparathyroidism (Cho et al., 2013).

Likewise, in a cross-sectional case-control study, hypoparathyroidism patients had significantly worse global complaint scores in several other validated QoL questionnaires (i.e., the Giessen Complaint List [p=0.036], von Zerssen Symptom List [p=0.002], and revised version Symptom Checklist 90 [p=0.020]), with predominant increases in the subscale scores for anxiety, phobic anxiety, and their physical equivalents, as compared with controls (matched for sex, age, and time since surgery) (Arlt et al., 2002).

2.3 Current Treatment

No formal guidelines or consensus statements have been developed to guide treatment of hypoparathyroidism, possibly due to the rarity of the disease and lack of effective treatments, therefore management of these patients is currently based on clinical experience and judgment (Bilezikian et al., 2011). Most hormone deficiencies are treated by replacement of the native hormone. Hypoparathyroidism is the last of the classic endocrine deficiency disorders to not have an approved hormone replacement therapy. The current standard-of-care for hypoparathyroidism is symptom management with pharmacological doses of oral calcium and active vitamin D (Table 12). Some patients also require adjunctive treatment with a thiazide diuretic, phosphate binder, and/or oral magnesium.

Table 12. Standard-of-Care for Chronic Treatment of Hypoparathyroidism

Agent	Formulation and Dose
Oral calcium[a]	Range from 1 to 9 gm/day elemental calcium and is usually given every 6 hours
• Calcium carbonate	40% elemental calcium by weight
• Calcium citrate[b]	21% elemental calcium by weight
Vitamin D metabolites[c]	
• Vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol)	25,000–100,000 IU once daily
• 1,25-dihydroxyvitamin D3 (calcitriol)	0.25–1.0 µg once or twice daily
• 1α-hydroxyvitamin D3 (alfacalcidiol)	0.5–3.0 µg (occasionally up to 5.0 µg) daily
• Dihydrotachysterol	0.2–1.0 mg once daily
Thiazide diuretics	
Hydrochlorothiazide or chlorthalidone	25-100 mg daily[d]
Phosphate binder	
Oral magnesium	
Magnesium oxide	400-500 mg once or twice daily[e]

a. The list of calcium preparations is not comprehensive. Of the calcium preparations available, only the carbonate and citrate salts contain sufficient elemental calcium (per tablet) for most patients with hypoparathyroidism. Other preparations may be used in patients who cannot tolerate citrate and carbonate salts. The percentage of elemental calcium is lower in these other preparations: calcium lactate (13%), calcium gluconate (9%), and calcium glubionate (6.6%); thus, larger numbers of tablets must be given.
b. Recommended in patients who have achlorhydria or who are taking a proton-pump inhibitor, in order to achieve sufficient absorption of calcium.
c. Vitamin D toxicity is an important concern and may occur at any time. Manifestations may include altered mental status, fatigue, thirst, dehydration, reduced renal function, nephrolithiasis, and constipation. Treatment involves discontinuation of the vitamin D preparation and the calcium salt. Depending on the severity, and especially if the toxic effects are from vitamin D metabolites with long half-lives, intravenous saline hydration and possibly oral glucocorticoids may be warranted to antagonize vitamin D action and more rapidly restore normocalcemia. Concentrations of 25-hydroxyvitamin D should be monitored, even in patients receiving calcitriol and alfacalcidiol to prevent vitamin D insufficiency. The target 25-hydroxyvitamin D concentration is 30 ng/mL or more.
d. Doses at high end of these ranges are usually needed to achieve substantial lowering of urinary calcium.
e. Until serum magnesium is maintained above 2 mg/dL
Source: Shoback, 2008, Bilezikian et al., 2011

The Mayo Clinic (http://www.mayoclinic.org/diseases-conditions/hypoparathyroidism/basics/treatment/con-20030780) and Johns Hopkins (http://www.hopkinsmedicine.org/healthlibrary/conditions/endocrinology/hypoparathyroidism_85,P00410/) recommend oral calcium and active vitamin D (ergocalciferol or calcitriol) as well as a diet rich in calcium and low in phosphorus to normalize both calcium and phosphorus serum concentrations.

The goals of chronic management of hypoparathyroidism are to maintain serum calcium and minimize hypocalcemia and the associated symptoms, while avoiding complications

of treating hypoparathyroidism with oral calcium and active vitamin D (Bilezikian et al., 2011; De Sanctis et al., 2012; Shoback, 2008):

- alleviate hypocalcemia and related symptoms – target serum calcium in low-normal range of approximately 8.0 to 8.5 mg/dL (2.00 to 2.12 mmol/L)
- lower hyperphosphatemia – target serum phosphorus in the high-normal range of 3.5 to 4.5 mg/dL (1.13 to 1.45 mmol/L)
- avoid hypercalciuria – maintain 24-hour urine calcium excretion < 300 mg/day
- maintain calcium-phosphate product < 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)

Calcium. Oral calcium dosing usually ranges from 1 to 9 grams of elemental calcium daily, divided in doses up to every 6 hours, either as calcium carbonate or calcium citrate (Bilezikian et al., 2011). For patients who require hospitalization for IV calcium, calcium gluconate is preferred (De Sanctis et al., 2012). Intravenous infusions are generally tapered slowly (over a period of 24 to 48 hours or longer) while oral therapy is adjusted (Shoback, 2008).

Most treatment recommendations for patients with hypoparathyroidism advise targeting a total serum calcium concentration in the lower end of the normal range – often between 8.0 and 8.5 mg/dL – and individually adjusting each patient's treatment. Oral calcium is typically initiated or adjusted when serum calcium drops below 7.5 mg/dL or in symptomatic patients (De Sanctis et al., 2012).

Vitamin D. Pharmacological management with vitamin D requires use of an activated form, such as 1,25 $(OH)_2D_3$, calcitriol. An active form of vitamin D overcomes hypoparathyroidism patients' lack of ability to convert native vitamin D to its active form. Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol), with longer half-lives, is often used in combination with the short-acting calcitriol to provide more consistent control over the course of the day.

Other Agents. Thiazide diuretics enhance distal tubular calcium reabsorption, thereby reducing urinary calcium excretion, and are thus sometimes useful in the treatment of hypoparathyroidism. Their use may limit the amount of vitamin D needed to maintain target serum calcium concentrations (Bilezikian et al., 2011). Patients with low serum magnesium should receive oral magnesium. Phosphate binders may also be helpful as adjunctive therapy in special situations (Shoback, 2008).

Management of hypoparathyroidism with oral calcium and active vitamin D addresses only the immediate "need" to increase serum calcium, and does not address the multiple abnormalities in physiological processes that occur in the absence of PTH in hypoparathyroidism, notably hypercalciuria, hypophosphaturia, and defective bone metabolism. Furthermore, they can result in hypercalcemia and hyperphosphatemia, and associated morbidities. Pill burden is substantial, with some patients requiring up to 80 tablets daily, with dosing at multiple time points during the day. Poor adherence leads to "swings" in patient symptoms.

2.4 Limitations of Current Management

While the goal of current treatment,consisting of pharmacological doses of calcium and active vitamin D, is to maintain serum calcium and minimize the symptoms of hypocalcemia, it does not address the physiologic aspects of hypoparathyroidism including metabolic bone abnormalities, hyperphosphatemia, and hypercalciuria. Calcium supplementation does not correct the underlying PTH deficiency and is associated with several challenges, including long-term complications from the use of these supplements without the underlying PTH hormone, which contributes to renal function deterioration, renal stones, and soft tissue calcifications (Aggarwal et al., 2013; Shoback, 2008).

In the long-term follow-up study of 120 patients with hypoparathyroidism (Mitchell et al., 2012) adverse renal effects were observed. In a subset of 53 patients with a 24-hour urine collection for calcium, 38% had at least one measurement over 300 mg/day (which reflects poor reabsorption, high tubular concentrations, and increased risk of tubular precipitation). Almost a third of patients with renal imaging (17/54) had renal calcifications. Rates of chronic kidney disease Stage 3 or higher were 2- to 17-fold greater than age-appropriate norms.

The risk of renal complications in patients with hypoparathyroidism was also evaluated in a case study using the Danish National Patient Registry and a prescription database. From 1988 to the present, 688 patients were identified who manifested symptoms of hypocalcemia and inappropriately low PTH levels following neck surgery that required oral calcium and/or active vitamin D. Compared with age- and sex-matched controls, patients with hypoparathyroidism had an increased risk of renal complications (hazard ratio: 3.67, 95% CI, 2.41 to 5.59) (Underbjerg et al., 2013).

Experts recommend close monitoring of patients being treated for hypoparathyroidism with large amounts of calcium and vitamin D preparations (Table 13) (De Sanctis et al., 2012; Shoback, 2008). Renal function, serum calcium and phosphate concentrations and urinary calcium should be closely monitored to minimize risks for hypocalemia, adverse renal effects and calcium-phosphate deposition into soft tissues. Soft tissue deposition is possible in the eye, kidney, brain and the cardiovascular system (structural dysfunction of blood vessels, myocardium, and heart valves) (Shoback, 2008; Kuhlmann 2006).

Table 13. Recommended Monitoring in the Management of Hypoparathyroidism

Parameter	Monitoring Interval
Serum calcium, phosphorus, creatinine	During Initial Dose Adjustment: Weekly to monthly After Treatment Stabilization: Twice yearly
Urine calcium and creatinine	Twice yearly
Ophthalmologic evaluation/slit lamp	Yearly

Source: Shoback, 2008.

2.5 Medical Need for Parathyroid Replacement Therapy

As noted above, oral calcium and active vitamin D – the current standard-of-care to manage hypoparathyroidism – do not address the multiple abnormalities in physiological processes that occur in the absence of PTH. PTH has a variety of critical physiological functions that include its central role in modulating serum calcium and phosphate concentrations within tightly controlled range, regulating renal calcium and phosphate excretion, activating vitamin D, and maintaining normal bone turnover (Figure 7).

Two formulations of PTH have been studied for the treatment of hypoparathyroidism – teriparatide (recombinant human PTH[1-34] by the NIH) and the full-length molecule recombinant human parathyroid hormone, rhPTH (1-84) (i.e., Natpara) – both administered by subcutaneous (SC) injection. Once daily dosing of Natpara provides an appropriate 24-hour calcemic response in hypoparathyroidism patients, whereas rhPTH(1-34) requires multiple injections per day (Cusano et al., 2012).

Replacement therapy with Natpara is a logical, physiologic replacement strategy to fulfill the current unmet medical need in the treatment of hypoparathyroidism. Natpara exhibits all the physiological effects of PTH; it can restore more normal calcium, phosphate, and vitamin D metabolism in subjects with hypoparathyroidism (Table 14) while significantly decreasing the requirement for oral calcium and active vitamin D.

Table 14. Treatment Effects in Hypoparathyroidism

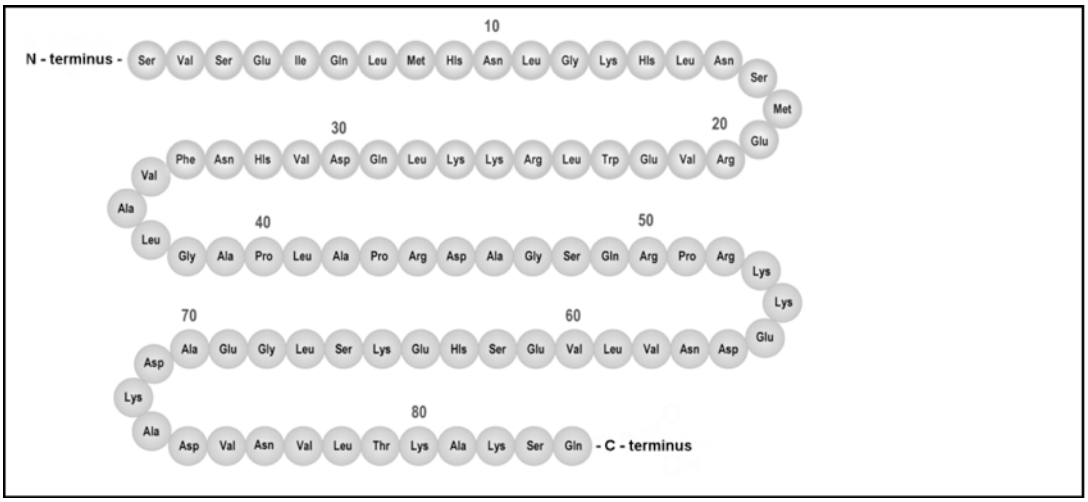
Action in Hypoparathyroidism	Calcium and/or Active Vitamin D	Natpara
Increase serum calcium concentrations	Yes	Yes
Promote renal calcium reabsorption	No	Yes
Decrease serum phosphate	No (could worsen)	Yes
Decrease calcium-phosphate product	No (could worsen)	Yes
$1,25(OH)_2$ vitamin D production	No, only provided orally	Yes
Normalize bone turnover	No	Yes

3 OVERVIEW OF NATPARA DEVELOPMENT PROGRAM

3.1 Chemical Structure, Mechanism of Action, and Manufacturing of rhPTH(1-84)

Recombinant human parathyroid hormone – rhPTH(1-84) (Figure 8) – is an exact, full-length replica of endogenous human PTH. Natpara is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid (rDNA) technology. No animal-sourced proteins are used in the manufacturing process.

Figure 8. Amino Acid Sequence of rhPTH(1-84)



Contamination with mammalian viruses, transmissible spongiform encephalopathy, or mycoplasma is unlikely and, even if such agents were introduced, no replication is expected in bacterial growth medium. Therefore, the primary adventitious agents considered to be potential contaminants of rhPTH(1-84) are fungi and non-*E. coli* bacteria. Control of potential adventitious agents in the manufacture of Natpara is exerted through control of raw materials, typical biological controls during the manufacturing process, and drug substance and drug product testing.

Two formulations of rhPTH(1-84) were used in development. With the exception of 2 initial safety and tolerability studies (PBR 930811 and PBR 930812) and 2 bioavailability studies in patients with osteoporosis (SH PTH-0001 and ALX1 11-821), all other studies used the to-be-marketed formulation.

Natpara (rhPTH[1-84]) for injection is supplied as a multiple dose, glass dual-chamber cartridge that is available in 4 nominal dosage strengths (25, 50, 75, or 100 µg). Depending on the dosage strength, each medication cartridge contains 0.40, 0.80, 1.21, or 1.61 mg rhPTH(1-84), 4.5 mg sodium chloride, 30 mg mannitol, and 1.26 mg citric acid monohydrate as a sterile lyophilized powder, with 1.13 mL of a sterile 3.2 mg/mL aqueous solution of m-cresol as the reconstitution diluent. Reconstitution results in a

nominal solution concentration of 0.35 mg/mL (25 µg/dose), 0.70 mg/mL (50 µg/dose), 1.05 mg/mL (75 µg/dose) or 1.40 mg/mL (100 µg/dose).

The disposable medication cartridge is designed for use with a reusable mixing device for product reconstitution (Natpara® Mixing Device) and a reusable pen injector for drug delivery (Natpara® Q-Cliq™) (Figure 9). The pen injector is designed to deliver a fixed volumetric dose targeted at 71.4 µL. Using the pen injector, each medication cartridge delivers 14 doses; each dose contains 25, 50, 75, or 100 µg of Natpara depending on the product dosage strength.

Figure 9. Natpara® Pen Injector and Mixing Device

Two drug delivery systems were used in the hypoparathyroidism program – the Ypsomed pen injector and then the Haselmeier pen injector (Natpara Q-Cliq). The Natpara Q-Cliq was developed specifically for Natpara and is the to-be-marketed pen injector.

The Natpara Q-Cliq (with a 31-G, 8 mm needle) was used in Study PAR-C10-005 which confirmed its bioequivalence to the Ypsomed pen. From February 2012 onward the Natpara Q-Cliq was used in the ongoing hypoparathyroidism Study PAR-C10-008 (referred to as RACE).

The Ypsomed pen and the Natpara Q-Cliq are identical with respect to the needle and design injection volume (71.4 µL), and use the same medication cartridge containing the to-be-marketed Natpara formulation. Study PAR-C10-005 demonstrated bioequivalence of rhPTH(1-84) 100 µg when injected SC using the Natpara Q-Cliq as compared to when injected SC using the Ypsomed pen. The shear imparted to the product is comparable between the two injection pens.

3.2 Nonclinical Development Findings

Safety nonclinical pharmacology studies with rhPTH(1-84) did not identify any safety findings of clinical significance. Safety pharmacology studies included the following:

- In vitro hERG
- Canine Purkinje fiber assays
- Blood pressure in conscious, normal rats
- Cardiac and circulatory functions in open-chest, anesthetized dogs
- A functional observational battery to assess effects on the central nervous system

The nonclinical toxicology program included single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and antigenicity studies. The nonclinical safety assessment of rhPTH(1-84) demonstrated a human safety margin based on chronic systemic exposure for general toxicity of at least 8.8- and 13.9-fold in rats and monkeys, respectively, based on area under the curve (AUC) comparisons.

Following chronic administration of rhPTH(1-84), changes were noted primarily in the kidney and bone. These were not unexpected based on the pharmacological activity of PTH and given the high doses of rhPTH(1-84) that were evaluated in animals that were euparathyroid.

3.2.1 Cardiovascular Safety

Safety pharmacology studies primarily evaluated the cardiovascular effects of rhPTH(1-84) since PTH(1-34) relaxes vascular smooth muscle and decreases blood pressure (Mok et al.,1989). These included in vitro hERG and canine Purkinje fiber assays, a study assessing blood pressure in conscious, normal rats, and a study evaluating cardiac and circulatory functions in open-chest, anesthetized dogs. A functional observational battery was also performed in rats to assess effects on the central nervous system. These safety pharmacology studies with rhPTH(1-84) did not identify any safety findings of clinical significance.

3.2.2 Renal Toxicity

In 6-month toxicology studies of rhPTH(1-84), nephrotoxicity was observed in rats, but only minor renal changes were noted in monkeys. In the rat study, renal toxicity was characterized by a dose-related increased incidence and severity of pelvic and tubular mineralization. The administration of rhPTH(1-84) normally leads to an increase in serum calcium concentrations, but, in the rat, serum calcium concentrations were generally reduced at the higher doses and urinary excretion of calcium was dose-dependently increased. One explanation for the finding is increased calcitonin secretion leading to increased urinary calcium excretion, a calcium homeostatic mechanism in the rat that efficiently controls rhPTH(1-84)-induced increases in serum calcium. Therefore, assessment of serum calcium is of little value in predicting the potential for renal injury

in the rat. However, blood urea nitrogen (BUN) values were elevated in males at doses ≥ 300 µg/kg/day beginning on Day 28 and were considered to be indicative of renal injury. The NOAEL was 50 µg/kg/day for renal toxicity with an exposure based on AUC approximately 8.8- to 10.2-fold greater than that observed in hypoparathyroidism patients receiving the clinical dose of 100 µg/day. Because calcium homeostasis in rats is different than in humans, the renal findings in this species are not considered to be relevant to humans.

In euparathyroid cynomolgus monkeys receiving daily SC doses up to 30 µg/kg/day rhPTH(1-84) for 6 months, there were no significant adverse effects observed in this study at any dose level. The renal changes were considered to be physiological rather than adverse effects. At the 30 µg/kg/day dose, the AUCs were 12.8 and 18.3 ng·hr/mL in males and females, respectively, which are approximately 14 to 20 times greater than the AUC at the clinical dose of 100 µg/day in hypoparathyroidism patients.

3.2.3 Carcinogenicity

In a 104-week carcinogenicity study in rats, rhPTH(1-84) was evaluated at doses of 10, 50, and 150 µg/kg/day. The systemic exposure at the no-carcinogenic effect dose of rhPTH(1-84) (10 µg /kg/day) was 3.3- to 4.8-fold greater (based on AUC) than the exposure observed in hypoparathyroidism subjects at the clinical dose of 100 µg/day. The lowest dose at which an rhPTH(1-84)-related increase in osteosarcoma was observed (50 µg/kg/day) occurred at an exposure margin of 19.2 (females) to 26.0 (males) based on exposure at the highest clinical dose of 100 µg/day.

Osteosarcoma is discussed in more detail in Section 6.4.6.

3.3 Summary of Clinical Pharmacology

The Natpara development program included evaluation of the pharmacokinetics and pharmacodynamics in hypoparathyroidism patients. The results characterize the pharmacokinetics, demonstrate physiologic effects on calcium and phosphate, and support a once-a-day dosing regimen for the treatment of hypoparathyroidism.

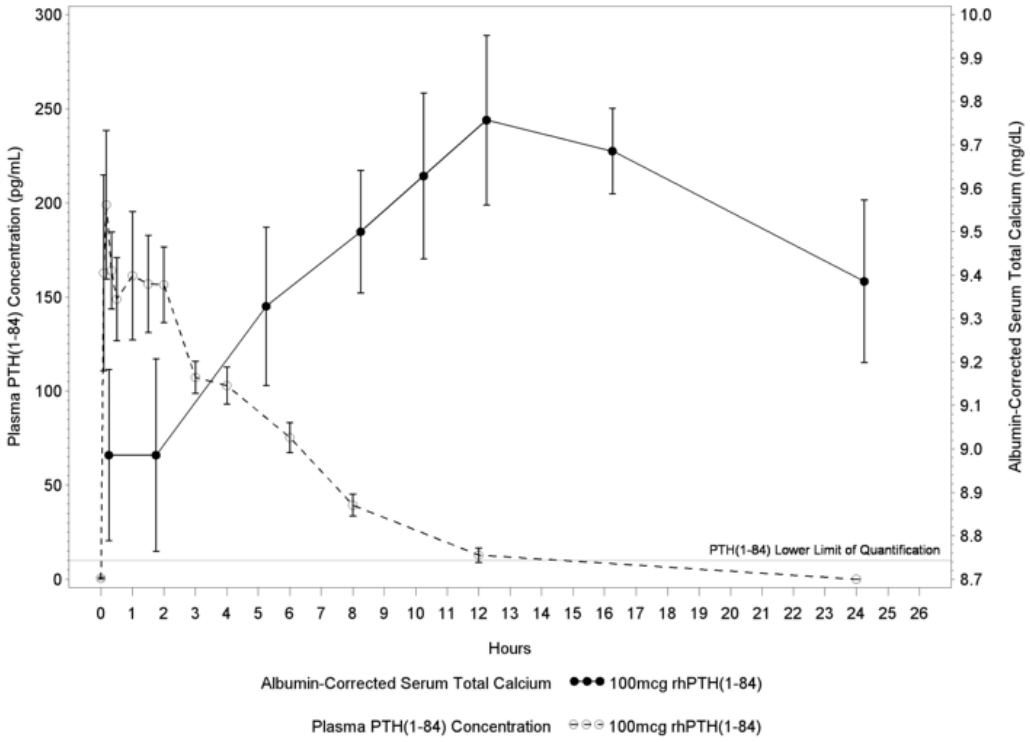
3.3.1 Pharmacokinetics

The pharmacokinetics of rhPTH(1-84) are linear and dose proportional over a dose range of 0.02 to 5 µg/kg. Following single SC injections of Natpara at 50 µg and 100 µg in subjects with hypoparathyroidism, peak plasma concentration (mean T_{max}) of PTH(1-84) occurred within 5 to 30 minutes and a second smaller peak at 1 to 2 hours. The plasma area under the curve (AUC) increased in a dose proportional manner from 50 µg to 100 µg. The apparent terminal half-life ($t_{1/2}$) was 3.0 and 2.8 hours for the 50 and 100 µg dose, respectively. The short peak in PTH(1-84) concentration following SC injection of Natpara is followed by a sustained increase in serum calcium, lasting 24 hours in hypoparathyroidism subjects (Figure 10).

Plasma concentration data from the long-term studies in subjects with hypoparathyroidism showed no accumulation of Natpara in the circulation and no

apparent change in the pharmacokinetics of Natpara after up to 15 months of daily therapy.

Figure 10. Mean (±SE) Unadjusted Plasma PTH(1-84) Concentration and Albumin-corrected Serum Total Calcium



SE = standard error
Note: Number of subjects = 7

Absorption:

In postmenopausal women, rhPTH(1-84) administered SC had an absolute bioavailability of 55%.

Distribution:

In postmenopausal women, rhPTH(1-84) following IV administration has a volume of distribution 5.35 L at steady state.

Metabolism:

In vitro and in vivo studies demonstrated that the clearance of PTH(1-84) is primarily a hepatic process with a lesser role played by the kidneys.

Excretion:

In the liver, most of the intact PTH(1-84) is cleaved by cathepsins. In the kidney, a small amount of PTH(1-84) binds to physiologic PTH-1 receptors, but most is filtered at the glomerulus. C-terminal fragments are also cleared efficiently by glomerular filtration.

Hepatic Impairment:

A pharmacokinetic study in non-hypoparathyroidism subjects was conducted in 6 men and 6 women with moderate hepatic impairment (Child-Pugh Classification of 7-9 [Grade B]) as compared with a matched group of 12 subjects with normal hepatic function. Following a single 100 µg SC dose, the mean maximum concentration (C_{max}) and baseline-corrected C_{max} values were 18% to 20% greater in the moderately-impaired subjects than in those with normal function. There were no apparent differences in the serum total calcium concentration-time profiles between the 2 hepatic function groups. No dose adjustment for Natpara is recommended in patients with mild to moderate hepatic impairment.

Renal Impairment:

The mean C_{max} of PTH following SC administration of a single 100 µg Natpara in subjects with mild-to-moderate renal impairment (creatinine clearance [CrCl] 30 to 80 mL/min) was approximately 22% higher than that observed in subjects with normal renal function (CrCl > 80 mL/min). Exposure to PTH as measured by $AUC_{0\text{-last}}$ and baseline-corrected $AUC_{0\text{-last}}$ was approximately 3.9% and 2.5%, respectively, higher than that observed for subjects with normal renal function. No dose adjustment is necessary in patients with mild to moderate renal impairment (CrCl 30 to 80 mL/min). No studies were conducted in patients on renal dialysis.

Population Pharmacokinetics:

Population pharmacokinetic findings suggest that no dose adjustments of Natpara are required in hypoparathyroidism (compared with non-hypoparathyroidism) subjects, according to sex (men versus women), or according to menopausal status (postmenopausal or premenopausal), age, weight, or classes of concomitant medications. However, in the clinical setting, any dose adjustments in the treatment of hypoparathyroidism are likely to be based primarily on the serum calcium concentration achieved.

The population pharmacokinetic model based on pharmacokinetic data collected in both hypoparathyroidism and osteoporosis clinical studies evaluated the potential effect of the presence of specific PTH(1-84) antibodies on pharmacokinetic parameters. In subjects with hypoparathyroidism, the elimination half-life ($t_{1/2}$) values of PTH(1-84) with presence of specific PTH antibodies was 1.6-fold longer than those without presence of specific PTH antibodies. However, based on the standard error estimated by NONMEM, the 95% confidence interval (CI) of this ratio included the null hypothesis (95% CI = 0.6-2.6). Therefore, the effect of presence of specific PTH antibodies on $t_{1/2}$ was not statistically significant.

3.3.2 Pharmacodynamics

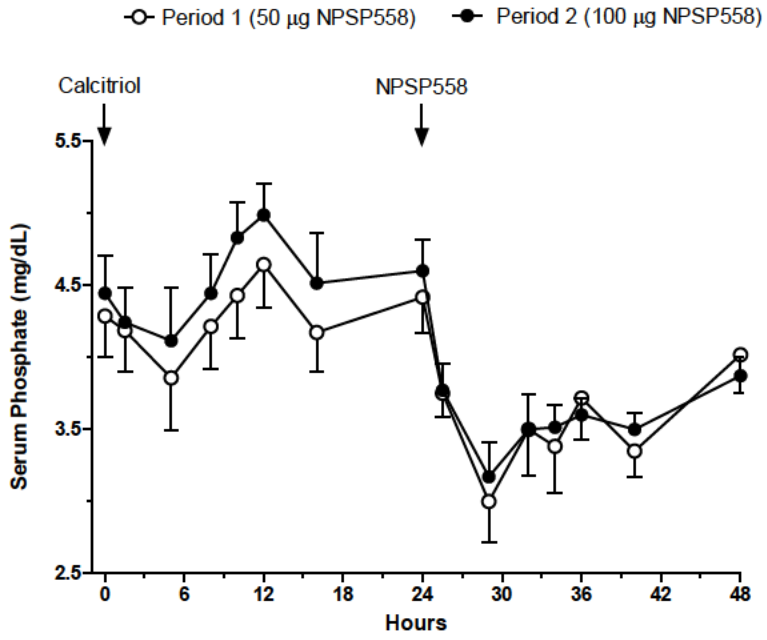
The pharmacodynamics of Natpara were evaluated in Study C09-002, an open-label, escalating, single-dose, multicenter study in which 8 subjects with a history of hypoparathyroidism received a single SC dose of Natpara, 50 µg during Period 1 and 100 µg during Period 2, with a ≥ 7-day washout interval between doses. Blood and urine sampling schedules were employed following Natpara administration on Day 1 in each period and during the 24-hours prior to each Natpara administration (Day -1) to assess the pharmacodynamic responses to the subject's habitual therapy (i.e., oral calcitriol). Calcitriol therapy was withheld on the days when Natpara was administered.

3.3.2.1 Serum Pharmacodynamics in Subjects with Hypoparathyroidism

Treatment with Natpara increased serum total calcium concentrations and decreased serum phosphate concentrations in subjects with hypoparathyroidism. The increase in serum total calcium concentrations occurred in a dose-related manner, with maximum mean increases (approximate 0.5 to 0.8 mg/dL) observed at approximately 12 hours. Mean concentration was sustained over baseline for more than 24 hours after administration (Figure 10).

Baseline serum phosphate levels began at close to the upper limit of the reference range and decreased by an average of 1.5 mg/dL to near the lower quartile of the reference range by 5 hours with both doses of Natpara. Serum phosphate had not returned to the elevated baseline concentrations by 24 hours with either dose (Figure 11).

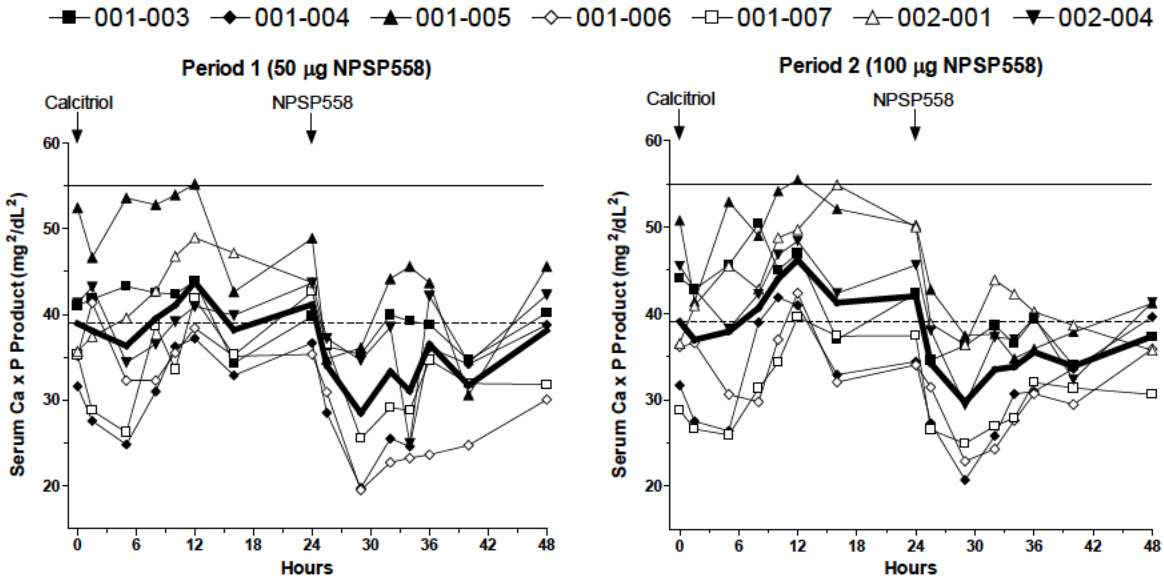
Figure 11. Mean (±SE) Serum Phosphate Concentrations Following Natpara Administration



NPSP558 = Natpara; SE = standard error
Note: Baseline resets to zero at 24 hours in each period
Period 1: N = 7 (0 - 24 hours); N = 6 (24 - 48 hours); Period 2: N = 7 (0 - 48 hours).

Despite an increase in serum total calcium levels, the decrease in serum phosphate levels with Natpara administration resulted in an overall decrease in the serum calcium-phosphate product, an important determinant of soft-tissue calcification (Figure 12).

Figure 12. Mean (±SE) Calcium-Phosphate Product Concentrations Following Natpara Administration

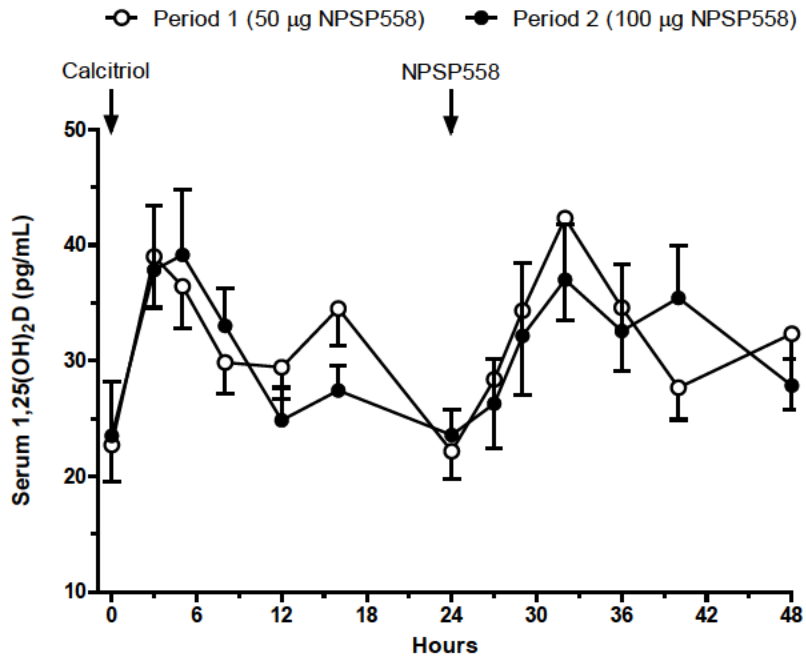


NPSP558 = Natpara; SE = standard error

Note: Shown are the serum calcium-phosphate product levels in each subject. The heavy solid lines show the mean values at each time point; the horizontal dotted lines show the mean serum calcium-phosphate product level prior to calcitriol administration in each period. The solid horizontal lines show the serum calcium-phosphate product level at which soft tissue calcification can occur more easily (>55 mg^2/dL^2).

Serum $1,25(OH)_2D$ increased to maximum concentrations between 8 and 12 hours with a return toward baseline concentrations by 24 hours (Figure 13). The increase was greater with the 50 µg dose possibly due to direct inhibition of the renal 25 hydroxyvitamin D-1-hydroxylase enzyme by serum calcium.

Figure 13. Mean (±SE) Serum 1,25-Dihydroxyvitamin D Concentrations Following Natpara Administration

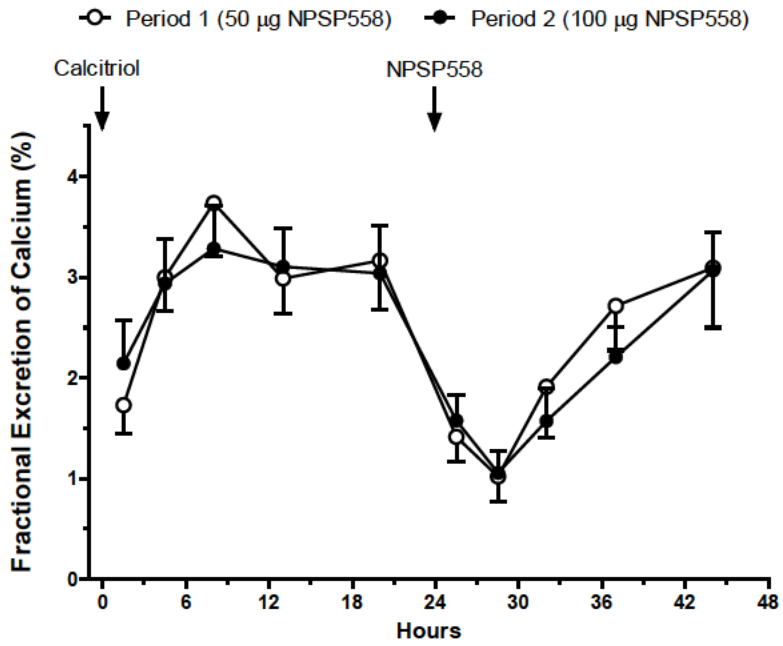


NPSP558 = Natpara; SE = standard error
Period 1: N = 7 (0 - 16 hours); N = 6 (24 - 48 hours); Period 2: N = 7 (0 - 48 hours).

3.3.2.2 Urine Pharmacodynamics in Subjects with Hypoparathyroidism

Also consistent with the physiologic effects of PTH, urinary calcium excretion was high at baseline and decreased by 65 to 68% at 3 to 6 hours following administration of both doses of Natpara, before increasing to predose levels in the 16- to 24-hour sample (Figure 14).

Figure 14. Mean (±SE) Urinary Fractional Excretion of Calcium Following Natpara Administration



NPSP558 = Natpara; SE = standard error
Note: Values shown are at the middle of each urine collection interval
Period 1: N = 7 (0 - 24 hours); N = 6 (24 - 48 hours); Period 2: N = 7 (0 - 48 hours).

Treatment with Natpara reduced total 24-hour urine calcium excretion by 13% and 23% following dosing with 50 µg and 100 µg, respectively (Table 15).

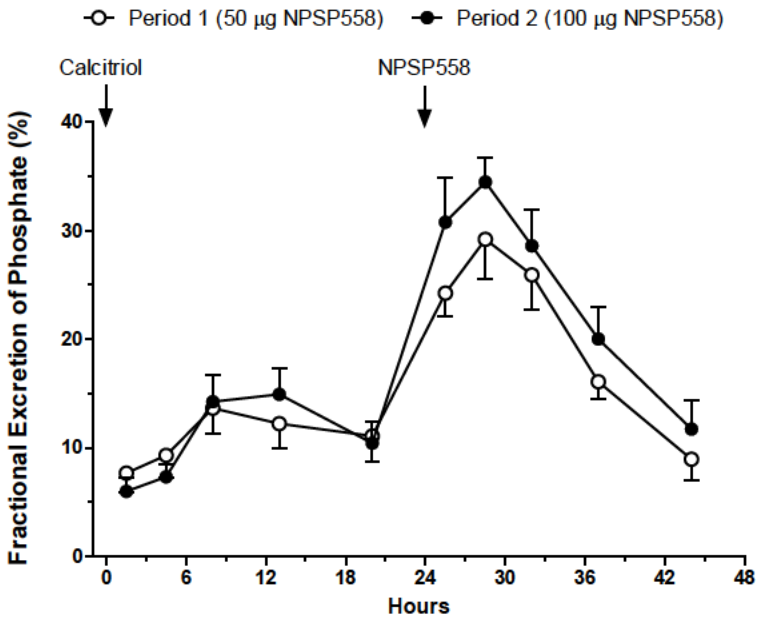
Table 15. Total Urinary Excretion of Calcium Over 24 Hours Following Administration of Calcitriol and Natpara

	Calcitriol 0.5-0.75 µg	Natpara 50 µg	Calcitriol 0.5-0.75 µg	Natpara 100 µg
	Day -1	Day 1	Day -1	Day 1
	(N = 7)	(N = 6)	(N = 7)	(N = 7)
Mean Calciuria mg (SD)	380 (121)	330 (165)	373 (163)	286 (131)

N = total number of subjects; SD = standard deviation

Baseline phosphate excretion was relatively low and increased 2.6- and 3.3-fold following administration of the 50 µg and 100 µg doses of Natpara, respectively, at 3 to 6 hours. Phosphate excretion returned to baseline levels in the 16- to 24-hour sample. Total 24-hour urinary phosphate excretion was increased by 51% and 60% with the 50 µg and 100 µg doses, respectively (Figure 15).

Figure 15. Mean (±SE) Urinary Fractional Excretion of Phosphate Following Natpara Administration



NPSP558 = Natpara; SE = standard error
Note: Values shown are at the middle of each urine collection interval.
Period 1: N = 7 (0 - 24 hours); N = 6 (24 - 48 hours); Period 2: N = 7 (0 - 48 hours).

3.3.3 Clinical Pharmacology Conclusions

The findings across all pharmacodynamic (PD) studies indicate that a single SC dose of Natpara normalized calcium, phosphate, and vitamin D metabolism lasting 24 hours, and reduced urinary calcium excretion in subjects with hypoparathyroidism, supporting a QD dosing regimen for the treatment of subjects with hypoparathyroidism, which is convenient and practical for patients as well as safe and effective for most patients with hypoparathyroidism. Once daily dosing of Natpara is also based on a pilot dose-finding study of 6-month effects on BTMs. In contrast, while calcitriol administration increased serum calcium levels, it either had no effect or tended to exacerbate other abnormalities in mineral homeostasis that occur in hypoparathyroidism (Figure 11 to Figure 15).

3.4 Regulatory History

NPS initially developed rhPTH(1-84) for the treatment of osteoporosis in postmenopausal women at a high risk of bone fracture submitting an investigational New Drug application to the Food and Drug Administration (FDA) on 31 January 1995. At the conclusion of the development program, NPS submitted an application on 10 May 2005 for rhPTH(1-84) with a proposed indication of "treatment of postmenopausal women with osteoporosis". The application received an approvable letter in March 2006, with key issues relating to safety associated with hypercalcemia and reliability of the delivery device used in the clinical trials. (The device that was the subject of FDA comments was different from that used in the hypoparathyroidism development program). The FDA required that an additional Phase 3 study be conducted to address these outstanding issues before NPS could obtain final approval for the osteoporosis indication. NPS did not pursue this route, changed its business model to focus on treatments for rare diseases, and later withdrew the osteoporosis application. Nonetheless, these data are informative and support the overall safety of Natpara.

In parallel with submission in the United States, a marketing authorization application for rhPTH(1-84) was submitted in European Union, and was approved in April 2006 (EU/1/06/339/001-002) for the therapeutic indication, "Treatment of osteoporosis in postmenopausal women at high risk of fractures." Nycomed A/S (now a Takeda company), the marketing authorization holder, commercialized rhPTH(1-84) at a daily SC dose of 100 µg under the proprietary name Preotact® in 15 countries. There was an estimated 61,091 patient years of exposure to Preotact from 24 April 2006 through 24 April 2013. The marketing application for Preotact was transferred from Takeda to NPS on 29 November 2013. NPS assessed the business opportunity for Preotact for the treatment of osteoporosis and decided to withdraw the authorization for commercial reasons.

FDA's involvement at key points in the clinical development of Natpara for hypoparathyroidism is summarized below:

- In 2007 the FDA granted Orphan Drug Designation for NPSP558 (the chosen designation for rhPTH[1-84]) for hypoparathyroidism.
- A pre-IND meeting with the Agency was held 17 December 2007 and the Agency noted in their minutes, dated 8 February 2008, that a primary endpoint consisting of achievement of eucalcemia while targeting a clinically significant reduction in the requirement for calcium and vitamin D is appropriate (as was used for the Phase 3 pivotal trial).
- At an 06 July 2010 Type C Advice meeting, agreement was reached with the Agency on the submission of Natpara as a drug-device combination and on a bridging strategy for the transition from the device initially used in the hypoparathyroidism clinical trials (Ypsomed pen injector) to the to-be-marketed US commercial mixing device (Natpara® Mixing Device) and pen injector (Natpara® Q-Cliq™) (Section 3.1).

- Agreement was reached with the Agency on a target exposure of 73 subjects treated for at least 12 months (19 from NPS-sponsored studies and the remainder from IIT studies) during a Type C Advice meeting held with the FDA on 26 September 2011. In that meeting, the Agency agreed that the marketing application in this orphan indication would rely on NPS's sponsored multinational Efficacy and Safety Studies in Hypoparathyroidism, and be supported by the data from 2 IITs in hypoparathyroidism, along with safety data from clinical trials and postmarketing experience in patients with osteoporosis.
- The FDA confirmed (letter dated 23 December 2011) that Natpara should be designated as a biologic, and accordingly, the submission for Natpara was a Biologic License Application (BLA) application for a biologic-device combination (superseding prior reference to a drug-device combination).

NPS submitted an application on 24 October 2013 for Natpara® (rhPTH[1-84]) as a replacement for PTH in the long-term treatment of hypoparathyroidism.

3.5 Description of Clinical Studies Examining Efficacy and Safety of Natpara in Subjects with Hypoparathyroidism

In addition to the 12 clinical pharmacology studies referenced in Section 3.3, the Natpara clinical development program for hypoparathyroidism includes 4 efficacy and safety studies in subjects with hypoparathyroidism.

Study CL1-11-040 (also known as REPLACE) provides the primary evidence of effectiveness of Natpara in stabilizing calcium while reducing oral calcium and active vitamin D doses.

The long-term benefit of Natpara in treating hypoparathyroidism was evaluated in RACE. RACE is an ongoing, long-term (12 months with an extension), open-label study of Natpara (flexible dosing: 25, 50, 75, and 100 µg) for the treatment of adult male and female subjects with hypoparathyroidism. The subjects must have previously completed Study PAR-C10-007 (referred to as RELAY; 8 weeks of active therapy) and/or REPLACE (24 weeks of treatment with study drug and the 4-week follow-up visit). The interim cutoff date for RACE in support of the Natpara BLA was 25 March 2013, which provided efficacy and safety data up to 52 weeks for a majority of subjects. This data has been updated for this document to include data up to 30 September 2013 with data up to 2 years for all safety and efficacy parameters except for bone indices.

All NPS-sponsored hypoparathyroidism studies are included in the safety database. The safety of Natpara for the treatment of hypoparathyroidism is also supported by data from 7 studies in osteoporosis, and postmarketing safety data on the use of Natpara in patients with osteoporosis.

There are also two published IIT studies, one conducted by Dr. John P. Bilezikian and one by Dr. Leif Mosekilde. These studies were conducted external to NPS; the findings have not been verified by NPS.

For the Mosekilde IIT, it is worthwhile to note that on the last day of study drug injection, subjects were offered participation in an NPS-sponsored 24-hour pharmacokinetic/pharmacodynamic study, the results of which were published (Sikjaer et al., 2012) and included in the Natpara BLA application.

Table 16 provides a detailed overview of each NPS-sponsored study in the Natpara hypoparathyroidism program and Figure 16 shows the flow of subjects across the NPS-sponsored studies of subjects with hypoparathyroidism. Of note, 60% of the 121 subjects treated with Natpara in the Efficacy and Safety Studies in Hypoparathyroidism were enrolled in North America.

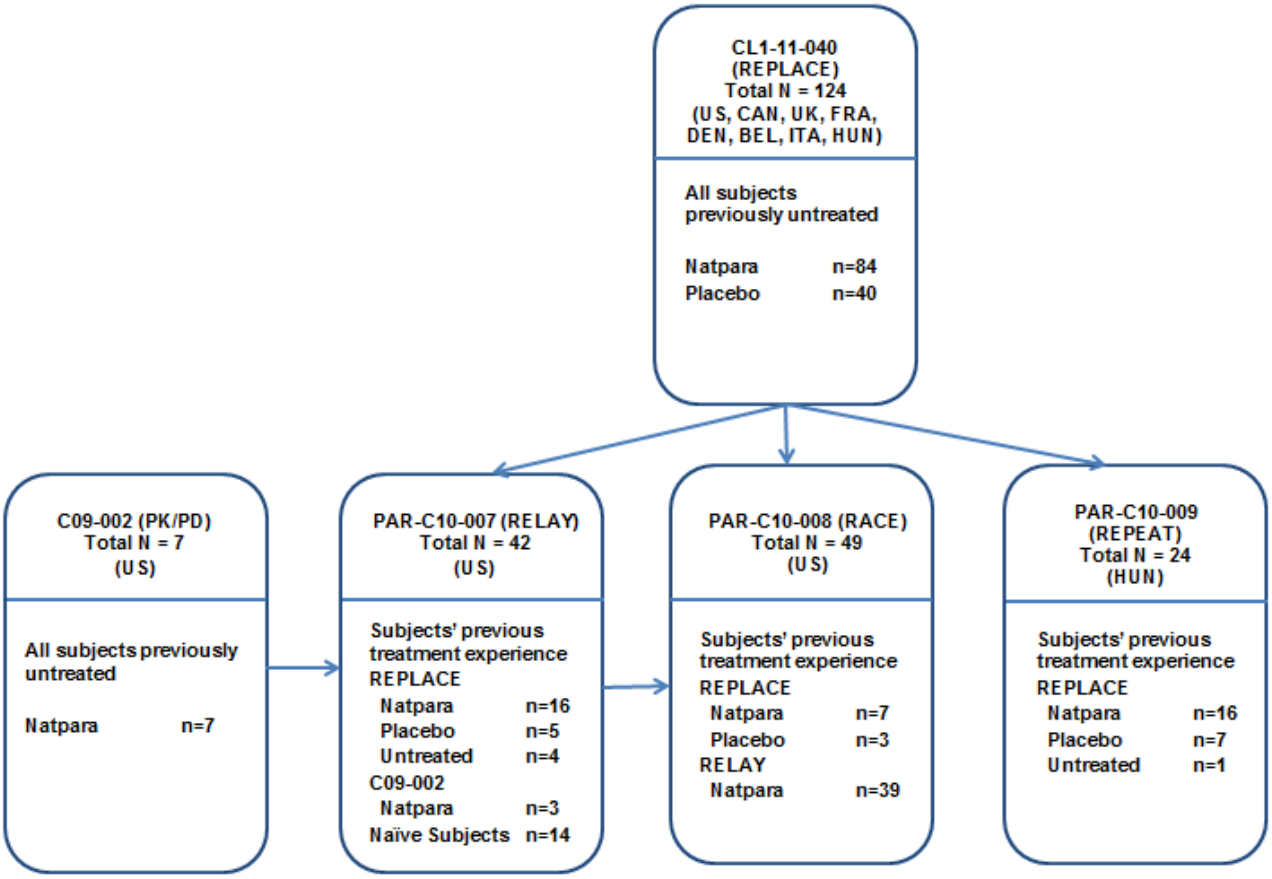
Table 16. Summary of Efficacy and Safety Studies in Subjects with Hypoparathyroidism

Study Number	Study Objectives	Study Design and Type of Control	Natpara Dose[a]	Number of Subjects	Duration of Treatment
CL1-11-040 (REPLACE)	Efficacy and Safety	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	Natpara, 84[b]; Placebo, 40[b]	24 weeks
PAR-C10-007 (RELAY)	Efficacy and Tolerability	Randomized, dose-blinded	25 or 50 µg (fixed doses)	42[b]	8 weeks
PAR-C10-008 (RACE)	Safety and Tolerability	Open-label	25, 50, 75, and 100 µg (flexible doses)	49[b]	52 weeks + extension **ONGOING**
PAR-C10-009 (REPEAT)	Safety and Tolerability	Open-label	50, 75, and 100 µg (flexible doses)	24	24 weeks

a. All doses of Natpara in the studies were a daily SC injection.

b. A total of 134 subjects were randomized into REPLACE (90 to Natpara and 44 to placebo). Total enrollment in RELAY was 47 subjects and in RACE, 53 subjects. A problem at 1 study site led to the necessity to exclude all data from 10 subjects enrolled at that site for REPLACE, 5 subjects enrolled in RELAY, and 4 subjects enrolled in RACE. Therefore, the Briefing Document presents data on the revised number of subjects displayed in this table.

Figure 16. Flow of Subjects Across Studies of Hypoparathyroidism



BEL=Belgium, CAN=Canada, DEN=Denmark, FRA=France, JUN=Hungary, ITA=Italy, UK=United Kingdom, US=United States

4 EFFICACY FINDINGS IN REPLACE

4.1 Study Methodology

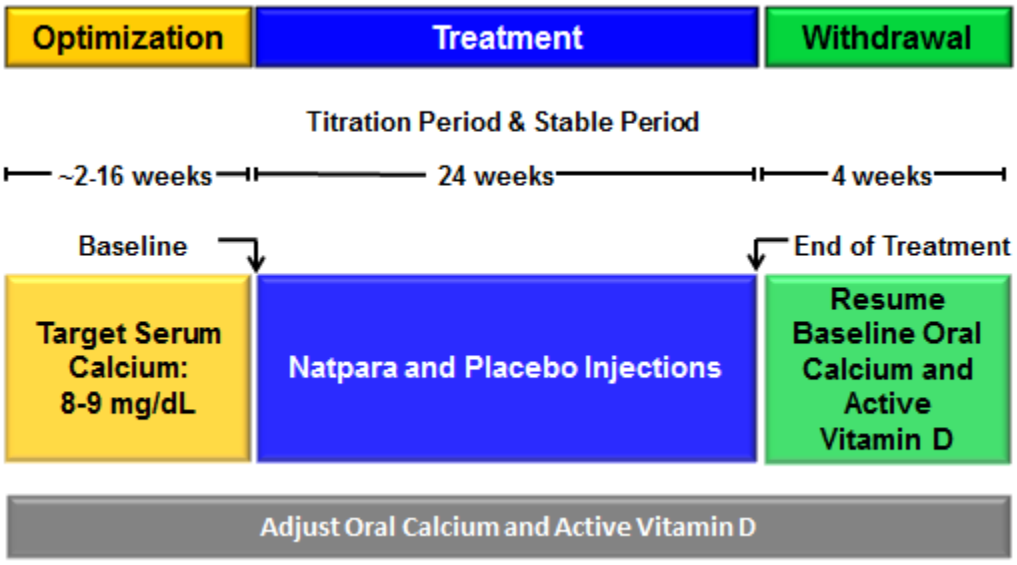
4.1.1 Study Design

REPLACE was a multinational, randomized, double-blind, placebo-controlled Phase 3 study in adult subjects (≥18 years old) with hypoparathyroidism. It is the largest randomized, controlled study ever conducted in a hypoparathyroidism population. The study was designed to show that Natpara is effective in maintaining serum calcium levels in the setting of reduced calcium and vitamin D supplementation. The study also evaluated symptoms as defined by adverse events as well as the physiologic effects of Natpara on hypercalciuria, hyperphosphatemia, and BTMs.

The study consisted of a 2- to 16-week optimization period during which calcium and active vitamin D therapies were optimized in terms of dose form and time of administration to achieve an albumin-corrected total serum calcium concentration of between 7.5 mg/dL and the upper limit of the laboratory normal range.

The optimization period was followed by subject randomization and a 24-week treatment period (Figure 17). Eligible subjects were randomized (2:1) to QD treatment with either SC Natpara or SC matching placebo.

Figure 17. Study Design – REPLACE



Only those subjects who completed the optimization period and met all of the following criteria were eligible for randomization:

- Their daily dose of calcium citrate was ≥ 1,000 mg and the daily dose of calcitriol was ≥ 0.25 µg, or the daily alphacalcidol dose was ≥ 0.50 µg.
- Two successive study visits separated by a 2-week interval were characterized by:
  - ≤ 25% change in the daily doses of both calcium citrate and active vitamin D and
  - the second of 2 serial albumin-corrected total serum calcium concentrations (as reported by the central laboratory) was the same or higher than the prior albumin-corrected total serum calcium value.
- The albumin-corrected total serum calcium concentration was between 7.5 mg/dL and the laboratory ULN.

The 24-week treatment period consisted of a 12-week titration period and a 12-week maintenance period. In the titration period, study drug was titrated during protocol-guided reduction in vitamin D and oral calcium. Efficacy was assessed at the end of the maintenance period.

The protocol provided specific directions on titration with subjects titrated to 1 of 3 Natpara doses (50 75, and 100 µg) based on serum calcium concentrations. A summary of the key targets follows:

- On Day 1, all subjects began treatment with study drug and had their active vitamin D dose reduced by 50%.
- Oral calcium and active vitamin D were decreased if serum calcium concentration was above 9 mg/dL.
- Oral calcium and active vitamin D were increased if serum calcium was below 8 mg/dL.
- Study drug was up-titrated to 75 µg after 2 to 3 weeks and oral active vitamin D and/or calcium were further reduced.
- Subjects were up titrated to 100 µg, if they had not achieved independence from active vitamin D and reduced oral calcium to 500 mg/day or less.

Down-titration of Natpara (in 25 µg decrements to not less than 50 µg QD) was permitted in the presence of hypercalcemia at any time during the study for subjects who were no longer taking oral calcium/active vitamin D. If a subject's serum calcium was below 8 mg/dL after 8 weeks of study drug dosing, the doses of oral calcium and active vitamin D were increased.

Subjects self-administered or underwent administration by a designee in the morning using identical-looking, multidose injection pen devices. Active vitamin D was taken in the morning after study drug injection and oral calcium was taken as needed throughout the day. The daily doses of calcium and active vitamin D metabolite/analog were

collected from site investigator prescription and from an electronic subject diary in which subjects recorded study drug administration/site, calcium, and vitamin D usage.

Upon discontinuation of study drug, subjects entered a 4-week post-treatment follow-up period to assess the impact of abrupt withdrawal. Oral calcium and active vitamin D were reinstated at baseline levels during the follow-up period. The initiation of the RELAY and RACE studies in 2011 provided an opportunity for US subjects who completed 28 weeks in REPLACE to enter RELAY and then RACE or to enroll directly into RACE. Study PAR-C10-009 (referred to as REPEAT; 24 weeks of treatment) was also initiated in 2011 for REPLACE subjects who were enrolled at 3 sites in Hungary.

4.1.1.1 Inclusion Criteria

Subjects who met the following inclusion criteria were eligible for study enrollment and randomization:

1. Adult males or females 18 to 85 years of age (prior to screening). Those < 25 years old were examined radiologically to ensure epiphyseal closure prior to randomization.
2. History of hypoparathyroidism for ≥ 18 months post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of the normal reference range (LLN) on 2 test dates at least 21 days apart within 12 months prior to randomization.
3. Requirement for vitamin D metabolite/analog therapy with calcitriol ≥ 0.25 µg QD or alphacalcidol ≥ 0.50 µg QD as well as oral calcium ≥ 1000 mg QD over and above normal dietary calcium intake prior to randomization.
4. Serum thyroid function tests were within normal laboratory limits at screening for all subjects not receiving thyroid replacement therapy. For subjects on thyroid replacement therapy, the dose was stable for at least 3 months prior to screening and the thyroxine value could have been outside the reference range.
5. Serum magnesium concentrations were within the reference range at the end of the optimization period. Subjects with low serum magnesium were to receive supplementation at a clinically appropriate level until the serum magnesium was within the reference range by the end of the optimization period and normal serum magnesium was to be maintained throughout the study.
6. Serum 25-hydroxyvitamin D concentration was ≤ 1.5-fold the upper limit of the normal reference range (ULN) at the end of the optimization period. Subjects with low serum 25(OH) D concentrations at screening received vitamin D during the optimization period. Subjects with serum 25(OH) D concentrations above the ULN had vitamin D withdrawn during the optimization period. Serum 25(OH) D concentrations that were within the reference range must have been confirmed by the end of the optimization period.

7. Creatinine clearance > 30 mL/min on 2 separate measurements or creatinine clearance > 60 mL/min and serum creatinine < 1.5 mg/dL by the end of the optimization period (prior to randomization).
8. Female subjects who were postmenopausal (absence of menses for ≥ 2 years with confirmed follicle stimulating hormone test) or were surgically sterilized could be enrolled, as could women of childbearing potential who had a negative pregnancy test at randomization and were willing to use 2 medically acceptable methods of contraception for the duration of the study and undergo pregnancy testing at every scheduled visit.

4.1.1.2 Exclusion Criteria

Subjects were not eligible for this study if any of the following applied:

1. Known history of hypoparathyroidism resulting from an activating mutation in the CaSR gene or impaired responsiveness to PTH (pseudohypoparathyroidism)
2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, such as active hyperthyroidism, Paget's disease, Type 1 or poorly controlled Type 2 diabetes mellitus (HbA1c > 8%), severe and chronic cardiac, liver or renal disease, Cushing's syndrome, neuromuscular disease such as rheumatoid arthritis, myeloma, pancreatitis, malnutrition, rickets, recent prolonged immobility, active malignancy, primary or secondary hyperparathyroidism, a history of parathyroid carcinoma, hypopituitarism, acromegaly, or multiple endocrine neoplasia types I and II
3. Disease-free for a period of less than 5 years for subjects with a history of thyroid cancer
4. Subjects dependent on regular parenteral calcium infusions (e.g., calcium gluconate) to maintain calcium homeostasis
5. Subjects who had undergone gastric resection or have active peptic ulcer disease requiring medical therapy
6. Use of prohibited medications within respective prohibited periods such as loop diuretics (30 days), thiazide diuretics (14 days), raloxifene hydrochloride (3 months), lithium (30 days), estrogens and progestins for replacement therapy (3 months), methotrexate (6 months), or systemic corticosteroids (3 months)
7. Previous treatment with PTH-like drugs, including PTH(1-84), PTH(1-34) or other N-terminal fragments or analogs of PTH or PTH-related protein within 6 months prior to screening

8. Other drugs known to influence calcium and bone metabolism, such as calcitonin and cinacalcet hydrochloride within 3 months and fluoride tablets within 6 months
9. Use of oral bisphosphonates within the previous 6 months or IV bisphosphonate preparations within the previous 12 months prior to screening
10. Seizure disorder/epilepsy with a history of a seizure within the previous 6 months prior to screening
11. Presence of open epiphyses
12. Irradiation (radiotherapy) to the skeleton within 5 years
13. Serum 25-hydroxyvitamin D concentrations greater than 1.5-fold the laboratory ULN prior to randomization
14. History of diagnosed drug or alcohol dependence within the previous 3 years
15. Clinical history of renal calculi within the past 12 months
16. History of gout or cerebrovascular accident
17. Disease processes that may adversely affect GI absorption, including but not limited to short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn's disease
18. Chronic/severe cardiac disease including but not limited to cardiac insufficiency, arrhythmias, bradycardia (resting heart rate < 60 beats/minute), or hypotension (systolic and diastolic blood pressures < 100 and 60 mmHg, respectively)

4.1.2 Clinical Endpoints

As the first registration trial to investigate PTH replacement for hypoparathyroidism, the REPLACE trial used a composite primary endpoint as well as secondary endpoints to demonstrate that Natpara could maintain serum calcium while replacing current therapy.

4.1.2.1 Primary Endpoint

A triple component primary efficacy endpoint was assessed at the EOT. This efficacy endpoint reflects a switch or replacement methodology that maintains serum calcium concentration while reducing or eliminating the need for oral calcium and active vitamin D administration. For a subject whose study treatment was still ongoing after Week 16, the combined endpoint of 3 components (listed below) had to be met at the EOT:

- at least a 50% reduction from the baseline oral calcium dose, and
- at least a 50% reduction from the baseline active vitamin D dose, and
- an albumin-corrected total serum calcium concentration that was maintained within a range of 7.5 to 10.6 mg/dL.

Subjects who discontinued treatment before Week 16 did not meet the endpoint. Subjects who discontinued treatment between week 16 and 24 were included in the analysis based upon assessment of each component.

The triple endpoint definition was selected based upon input from clinical experts. A 50% reduction in both calcium and active vitamin D doses while maintaining serum calcium concentration was chosen as this was considered a clinically meaningful reduction.

4.1.2.2 Key Secondary Endpoints

The secondary efficacy variables were based on, in order (following a fixed sequence test procedure described in Section 4.1.2.4.2):

- Percent reductions in calcium dose at Week 24
- Proportion of subjects who achieved independence from active vitamin D metabolite/analog usage and a calcium dose of ≤ 500 mg/day or less by Week 24
- The frequency of clinical symptoms of hypocalcemia (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24

The first 2 secondary endpoints characterized the individual components of the primary endpoint. The third endpoint was an effort to understand the prespecified hypocalcemia symptoms to assess benefit in subjects who had achieved optimal serum calcium targets. The targeted serum calcium levels reflect "best" treatment of hypocalcemia as recommended in the current literature.

Symptoms of hypocalcemia were identified as follows. After database lock, clinical experts/key opinion leaders medically reviewed a blinded list of TEAEs (generated by MedDRA system organ class and preferred term) to identify AE terms that were classified into a group of medical synonyms that best defined symptoms of hypocalcemia. The blinded list was further refined by NPS clinical review and the resulting list was used in analysis. The MedDRA AEs were agitation; anxiety; back pain; blepharospasm; facial spasm; hypoaesthesia, including facial, and oral; irritability; muscle fatigue; muscle spasms; muscle tightness; muscle twitching; musculoskeletal pain; musculoskeletal stiffness; myalgia; nervousness; oesophageal spasm; paresthesia, including oral; tetany; throat tightness; and tremor.

4.1.2.3 Prespecified Exploratory Endpoints

The prespecified exploratory endpoints examined the clinical meaningfulness of the key efficacy findings.

- Proportion of subjects that demonstrated at least a 50% reduction from baseline amounts of oral calcium and at least a 50% reduction from baseline amounts of active vitamin D therapy by Week 24 of the study and an albumin-corrected total serum calcium concentration at each of the Week 16, Week 20, and Week 24 assessments that was maintained or normalized compared to the baseline value (for Amendment 7, this was defined as ≥ 7.5 mg/dL; prior to Amendment 7, this

was defined as comparable to the baseline value) and did not exceed the upper limit of the laboratory normal range

- Change from baseline in 24-hour urine calcium excretion at Week 24
- Proportion of subjects who had a calcium-phosphate product in the normal range of ≤ 55 mg^2/dL^2 at Week 24
- Change in BMD by dual energy x-ray absorptiometry of the lumbar vertebra (L1-L4), hip (total, trochanter, intertrochanter, Ward's triangle and femoral neck) and distal one-third radius at Week 24 compared to baseline
- Change from baseline in BTMs bone-specific alkaline phosphatase, serum carboxy-terminal telopeptide of type I collagen, procollagen amino terminal peptide (BSAP, s-CTx, P1NP, respectively), and osteocalcin at Week 24
- Change in quality of life score as measured using the SF-36 Questionnaire from baseline to Week 24

4.1.2.4 Statistical Methods

4.1.2.4.1 Sample Size

A sample size (including potential dropouts) of 110 adult male and female subjects was estimated assuming the following:

- A 2:1 randomization for active study drug or placebo
- Approximately 84 (56 active and 28 placebo) subjects complete the study
- 40% of subjects in the Natpara group meeting the primary endpoint
- 10% of subjects in the placebo group meeting the primary endpoint
- 80% power based on 2-tailed test and alpha of 0.05.

4.1.2.4.2 Randomization and Blinding

A simple block randomization (2:1 ratio for rhPTH[1-84] and placebo) was applied study wide without use of stratification factors. The randomization schedule was implemented via an IVRS system.

Study medications were administered in a double-blind fashion throughout the study execution. During the study unblinding was only allowed, with the approval of the responsible NPS medical monitor, if a subject became pregnant or seriously ill. These events did not occur during this study. Specific lab results, including bone turnover marker and PTH levels, were blinded to NPS and study site personnel.

4.1.2.4.3 Statistical Analyses

All efficacy analyses were conducted on the intent-to-treat (ITT) population. The ITT population included all randomized subjects who received at least one dose of study drug and had at least one post-baseline efficacy measurement.

A fixed sequence test procedure was used to control the study level type I error. The order of test sequence started with the primary efficacy endpoint and proceeded to the 3 secondary efficacy endpoints, in the order in which the secondary efficacy endpoints were defined. Analyses were conducted with a type I error of 0.05. Any subsequent hypothesis tests were not executed unless all precedent tests in the sequence resulted in statistically significant results (i.e., $p < 0.05$).

Primary Endpoint Analyses

A 2-sided Fisher's Exact test was utilized to test the difference in proportions meeting the triple endpoint between treatment groups. The difference and its 2-sided asymptotic 95% confidence interval (CI) were presented. For assessment of the daily doses of calcium and active vitamin D metabolite/analog, investigator-prescribed data were defined by protocol as primary for all efficacy analyses.

The protocol specified multiple supportive analyses that were reported in the clinical study report and not necessary in this Briefing Document. For the primary endpoint, the analyses included percentage of subjects meeting the primary endpoint by study visit from Visit 7 (Week 2); time to first response at each scheduled visit; mixed-effect model repeated measure analysis of percentage of subjects meeting the primary endpoint at EOT based on subject diary data; analysis based on investigator-prescribed and subject diary data, using unadjusted total serum calcium; percentages of subjects meeting the primary endpoint (based on investigator-prescribed data and on subject diary data) in the placebo and Natpara treatment groups at each week that a study visit occurred during the treatment period; and, analyses for 2 of the 3 primary endpoint criteria (i.e., calcium criteria response and vitamin D criteria response) based on investigator-prescribed data and on subject diary data.

Prespecified subgroup analyses were also conducted, including subgroups of age (< 45, 45 to 64, ≥ 65), sex, geographic region (North America, Western Europe, and Hungary), prescribed active vitamin D dose at baseline (high dose, medium dose, and low dose); prescribed calcium dose at baseline (0 to 2000 mg/day, > 2000 mg/day), and duration of hypoparathyroidism (≤ 5 years, > 5 to 10 years, > 10 years). In these analyses, active vitamin dose-level designations were defined as: for calcitriol: low dose 0 to 0.25 µg/day, medium dose > 0.25 to 0.5 µg/day, high dose > 0.5 µg/day; for alphacalcidol: low dose 0 to 0.50 µg/day, medium dose > 0.50 to 1.0 µg/day, high dose > 1.0 µg/day. Times to first response by visit based on investigator-prescribed data and subject diary data were summarized.

Sensitivity analyses were performed for the primary analysis based on the inclusion of all randomized subjects, treating any withdrawal prior to Week 16 as not meeting the

primary endpoint, investigator-prescribed and subject diary data at end of treatment,a summary of response rates using a mixed-effect model repeated measure, various percentages of reduction (from 10% to 90% in increments of 10%) in daily doses of calcium and active vitamin D, subjects who completed the treatment, imputation of diary data at EOT, and different maintenance ranges for ACSC concentration.

Secondary Efficacy Endpoint Analyses

The order of testing for the secondary endpoints is listed below, with hypothesis testing executed if all precedent tests in the sequence resulted in statistically significant results (i.e., $p < 0.05$).

- Percent reductions in calcium dose at Week 24
- Proportion of subjects who achieved independence from active vitamin D metabolite/analog usage and a calcium dose of ≤ 500 mg/day or less by Week 24
- The frequency of clinical symptoms of hypocalcemia (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24

The daily calcium dose based on investigator-prescribed data was the primary computation method used and subject diary data was used in a supportive analysis. For percentage change in calcium, treatment group differences were compared using an analysis of covariance (ANCOVA) with treatment as a factor and baseline calcium dose as a covariate.

The number and percentage of subjects achieving independence from active vitamin D metabolite/analog while maintaining calcium at a dose of 500 mg/day or less, and the number and percentage of subjects with clinical symptoms of hypocalcemia during Week 16 to Week 24 were presented by treatment group. For these 2 endpoints the proportions for the 2 treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test. The p-value was reported and the odds ratio between the treatments and its associated 95% CI were calculated.

Exploratory Efficacy Endpoint Analyses

Exploratory analyses were performed utilizing the following statistical methods:

- The CMH test was used with computation of p-values reported and odds ratio between the treatments and 95% CI.
- ANCOVA was used with treatment as a factor and baseline 24-hour urine calcium secretion as a covariate. The p-value for treatment effect was computed. The least-square (LS) means and standard error, along with 95% CI were presented for each treatment.
- Absolute value and change from baseline was summarized by visit and by treatment group. Treatment group differences were compared using an ANCOVA

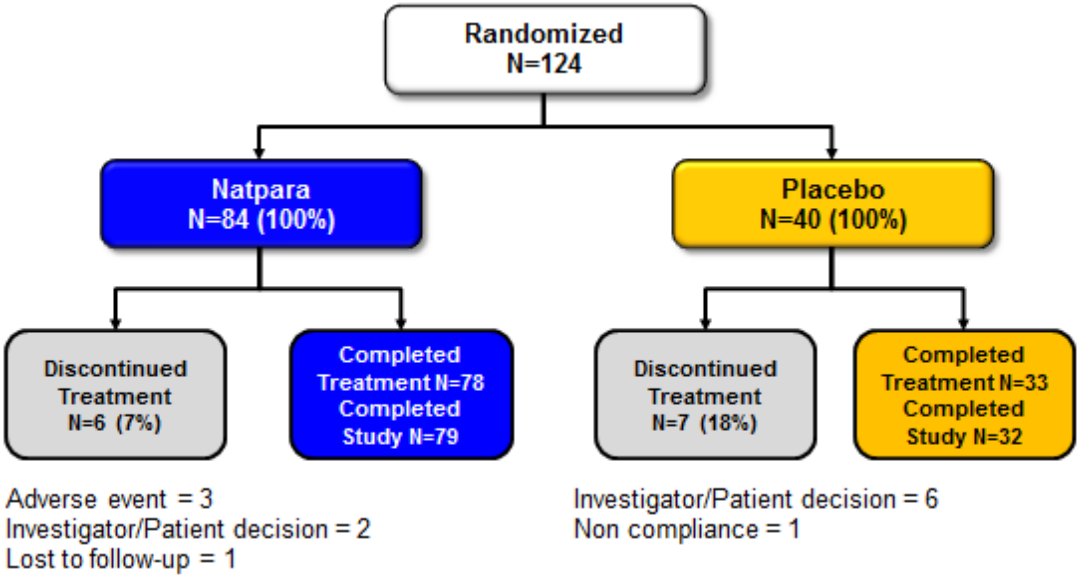
with change from baseline as the dependent variable, treatment as a factor, and baseline score as a covariate.

4.2 Subject Disposition

A total of 134 subjects were randomized into REPLACE, 90 to Natpara and 44 to placebo. A problem at 1 study site led to the necessity to exclude all data from 10 subjects enrolled at that site. Therefore, the Briefing Document presents data on 84 Natpara and 40 placebo subjects in REPLACE. Of note, the REPLACE efficacy and safety results based on the analyses reported herein (i.e., excluding subjects this site) are highly consistent with the results from analyses conducted in a data set that included all subjects.

A total of 28 sites randomized 124 subjects (Figure 18). Of the 84 subjects randomized to Natpara, 78 completed the treatment period and 79 completed the 4-week follow-up period (i.e., completed the study). Of the 40 subjects randomized to placebo, 33 completed the treatment period and 32 completed the 4-week follow-up period.

Figure 18. Subject Disposition –REPLACE



Note: In the placebo group, 3 subjects discontinued participation in the study due to the investigator's decision after it was determined that the subjects were noncompliant with study procedures. In the Natpara group, 1 subject missed only the last dose of study drug due to an adverse event of rash and is included in discontinuations from treatment, but counted as a study completer as she continued into the 4-week follow-up period.

Of the 84 subjects in the Natpara treatment group, 18 were up-titrated from 50 to 75 µg SC highest daily dose and 61 were up-titrated to 100 µg SC highest daily dose; 21 were down-titrated from their highest doses. The final dose of Natpara was 100 µg SC daily in

47 subjects (of 84, 56.0%) subjects, 75 µg SC daily in 22 subjects (26.2%), and 50 µg SC daily in 15 (17.9%) subjects.

4.3 Baseline Characteristics

The treatment groups were well balanced at baseline based on demographics, clinical disease characteristics, and geographic region of enrollment (52% North America, 48% Europe) (Table 17, Table 18, Table 19). Hypoparathyroidism was a postsurgical sequela for most subjects (71.8%) with a mean duration of disease that exceeded 10 years (mean 13.6 ± 10.34 years). In general, all subjects had baseline BMD (Table 17) and Z-scores that indicated a high BMD, reflecting low bone turnover.

At randomization, high-dose active vitamin D (calcitriol >0.5 µg/day or alphacalcidol >1.0 µg/day) was prescribed in 67% (56/84) of Natpara subjects and 63% (25/40) of placebo subjects. The calcium dose prescribed exceeded 2000 mg/day in 32% (27/84) of subjects in the Natpara group and 28% (11/40) of subjects in the placebo group.

At screening, mean 24-hour calcium excretion was 269 mg/24 hr and mean albumin-corrected serum calcium was 8.1 mg/dL; whereas after optimization with oral calcium and active vitamin D, baseline mean 24-hour urinary calcium excretion was elevated but similar in the 2 treatment groups (361 and 339 mg/24hr in the Natpara and placebo groups, respectively) and mean albumin-corrected serum calcium was 8.5 and 8.6 mg/dL in the Natpara and placebo groups, respectively (Table 18).

Table 17. Demographics and Baseline Characteristics – REPLACE

Variable	Placebo N=40	Natpara N=84	Total N=124	p-value
Mean age (SD) at Screening (years)	48.9 (13.76)	46.6 (12.18)	47.3 (12.70)	0.355
Sex[a], n (%)				
Female	33 (82.5)	65 (77.4)	98 (79.0)	0.513
Male	7 (17.5)	19 (22.6)	26 (21.0)	
Race, n (%)				
White	39 (97.5)	80 (95.2)	119 (96.0)	0.785
Height (cm)				
Mean (SD)	165.0 (8.27)	167.5 (8.83)	166.7 (8.69)	0.150
Weight (kg)				
Mean (SD)	78.9 (16.38)	82.1 (18.57)	81.1 (17.89)	0.360
Body mass index (kg/m^2)				
Mean	28.9 (5.30)	29.3 (6.43)	29.2 (6.07)	0.756
Geographic region of enrollment[b], n (%)				
North America	21 (52.5)	43 (51.2)	64 (51.6)	0.978
Western Europe	12 (30.0)	25 (29.8)	37 (29.8)	
Hungary	7 (17.5)	16 (19.0)	23 (18.5)	

Table 17. Demographics and Baseline Characteristics – REPLACE

Duration of hypoparathyroidism (years)				
Mean (SD)	11.6 (8.12)	14.6 (11.16)	13.6 (10.34)	0.124
Prescribed active vitamin D at baseline[c], n (%)				
Low Dose	3 (7.5)	6 (7.1)	9 (7.3)	0.896
Medium Dose	12 (30.0)	22 (26.2)	34 (27.4)	
High Dose	25 (62.5)	56 (66.7)	81 (65.3)	
Prescribed calcium at baseline, n (%)				
0 - 2000 mg/day	29 (72.5)	57 (67.9)	86 (69.4)	0.600
> 2000 mg/day	11 (27.5)	27 (32.1)	38 (30.6)	

ANOVA = analysis of variance; N = total number of subjects; n = number of subjects in subcategory; SD = standard deviation

Notes: Percentages are based on the number of subjects in each treatment arm. p-values for overall treatment comparisons are based on the chi-square test for categorical variables and on a one-way ANOVA with effect for treatment for continuous variables.

a. One subject had sex transformation before study enrollment.
b. North America includes Canada and the United States. Western Europe includes France, Italy, Belgium, Denmark, and the United Kingdom.
c. For calcitriol: low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day; for alphacalcidol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day

Table 18. Albumin-corrected Serum Calcium, Phosphate, Magnesium and Urinary Calcium at Baseline – REPLACE

Variable	Placebo N=40	Natpara N=84
Baseline albumin-corrected serum calcium, mg/dL		
Mean (SD)	8.6 (0.62)	8.5 (0.83)
Baseline serum phosphate, mg/dL		
Mean (SD)	4.5 (0.66)	4.5 (0.66)
Baseline serum magnesium, mg/dL		
Mean (SD)	2.0 (0.18)	2.0 (0.20)
Baseline urinary calcium, mg/24h		
Mean (SD)	338.5 (171.79)	361.1 (193.92)

Max = maximum; Min = minimum; N =total number of subjects; SD = standard deviation

Notes: Percentages are based on the number of subjects in each treatment arm.

Table 19. Etiology of Hypoparathyroidism – REPLACE

Etiology	Placebo N=40			Natpara N=84			Total N=124		
	Childhood[a] n (%)	Adult[a] n (%)	All Ages n (%)	Childhood n (%)	Adult n (%)	All Ages n (%)	Childhood n (%)	Adult n (%)	All Ages n (%)
Postsurgical	0	29 (72.5)	29 (72.5)	5 (6.0)	55 (65.5)	60 (71.4)	5 (4.0)	84 (67.7)	89 (71.8)
Thyroidectomy	0	28 (70.0)	28 (70.0)	4 (4.8)	51 (60.7)	55 (65.5)	4 (3.2)	79 (63.7)	83 (66.9)
Autoimmune thyroiditis	0	1 (2.5)	1 (2.5)	0	0	0	0	1 (0.8)	1 (0.8)
Basedow's disease	0	4 (10.0)	4 (10.0)	2 (2.4)	6 (7.1)	8 (9.5)	2 (1.6)	10 (8.1)	12 (9.7)
Goitre	0	4 (10.0)	4 (10.0)	0	7 (8.3)	7 (8.3)	0	11 (8.9)	11 (8.9)
Larynx cancer	0	0	0	0	1 (1.2)	1 (1.2)	0	1 (0.8)	1 (0.8)
Thalassaemia	0	0	0	0	1 (1.2)	1 (1.2)	0	1 (0.8)	1 (0.8)
Thyroid cancer	0	7 (17.5)	7 (17.5)	1 (1.2)	18 (21.4)	19 (22.6)	1 (0.8)	25 (20.2)	26 (21.0)
Unknown	0	12 (30.0)	12 (30.0)	1 (1.2)	18 (21.4)	19 (22.6)	1 (0.8)	30 (24.2)	31 (25.0)
Parathyroidectomy	0	1 (2.5)	1 (2.5)	1 (1.2)	4 (4.8)	5 (6.0)	1 (0.8)	5 (4.0)	6 (4.8)
Autoimmune hypoparathyroidism	0	1 (2.5)	1 (2.5)	1 (1.2)	0	1 (1.2)	1 (0.8)	1 (0.8)	2 (1.6)
Di George syndrome	1 (2.5)	0	1 (2.5)	2 (2.4)	0	2 (2.4)	3 (2.4)	0	3 (2.4)
Idiopathic hypoparathyroidism	1 (2.5)	8 (20.0)	9 (22.5)	6 (7.1)	15 (17.9)	21 (25.0)	7 (5.6)	23 (18.5)	30 (24.2)
Total	2 (5.0)	38 (95.0)	40 (100.0)	14 (16.7)	70 (83.3)	84 (100.0)	16 (12.9)	108 (87.1)	124 (100.0)

N = total number of subjects; n = number of subjects in subcategory

a. Based on each subject´s onset age of hypoparathyroidism, which is calculated as Age at Screening-Duration of Hypoparathyroidism. Childhood is defined as <18 years of age, adult is defined as ≥18 years of age.

Notes: Percentages are based on the number of subjects in each treatment arm.

4.4 Primary Endpoint

Overall, 46 subjects (54.8%) in the Natpara group and 1 subject (2.5%) in the placebo group achieved the primary efficacy triple endpoint at the EOT (calcium and vitamin D dose reduction of at least 50% while maintaining serum calcium in the target range). The treatment difference in response was 52.3% (95% CI for the treatment difference: 40.6% to 64.0%, $p < 0.001$; Table 20), showing superiority of Natpara.

The primary analysis was based upon investigator-prescribed data on calcium and vitamin D dosing, but the findings were similar when subject diary data were used in analysis. In the Natpara group, 46 of 84 (54.8%) met the primary endpoint compared to 1 of 40 (2.5%) in the placebo group ($p < 0.001$ for difference between groups).

Table 20. Analysis of Triple Endpoint at End of Treatment Based on Investigator-prescribed Data (Primary Endpoint) – REPLACE

	Placebo (N= 40)		Natpara (N= 84)		Treatment Difference	
Status	**n (%)**	**(95% CI)[a]**	**n (%)**	**(95% CI)[a]**	**(95% CI)[b]**	**p-value[c]**
Met endpoint	1 (2.5)	(0.1, 13.2)	46 (54.8)	(43.5, 65.7)	52.3 (40.6, 64.0)	< 0.001
Did not meet endpoint	39 (97.5)		38 (45.2)			

CI = confidence interval; N = total number of subjects; n = number of subjects in subcategory
Note: Percentages are based on the number of subjects in each treatment arm.
a. Based on exact 95% CI.
b. Treatment difference is calculated as percentage of subjects meeting the primary endpoint in the Natpara group minus the percentage of subjects meeting the primary endpoint in the placebo group; the 2-sided asymptotic 95% CI is based on normal approximation.
c. Based on Fisher's Exact test.

A statistically significantly greater percentage of subjects meeting the primary endpoint in the Natpara group as compared with the placebo group (investigator-prescribed and subject diary data) was also seen in all sensitivity analyses (described in Section 4.1.2.4.2; data not presented in this Briefing Document) and in all subgroup analyses (Table 21; all $p < 0.001$ based on Cochran-Mantel-Haenszel general association test). In addition to the subgroups displayed in Table 21, the number and percentage of Natpara-treated subjects who met the triple endpoint was calculated based on the etiology of hypoparathyroidism (surgical vs nonsurgical). Out of 60 subjects in the REPLACE study who developed postsurgical hypoparathyroidism, 35 subjects (58.3%) met the primary endpoint. Eleven of 24 (45.8%) subjects who had non-surgical etiologies of hypoparathyroidism met the primary endpoint.

Table 21. Analysis of Subjects Who Met the Primary Triple Endpoint at End of Treatment by Subgroup Based on Investigator-prescribed Data – REPLACE

	Placebo N= 40		Natpara N= 84		Treatment Difference	
Subgroup[d]	**n (%)**	**(95% CI)[a]**	**n (%)**	**(95% CI)[a]**	**(95% CI)[b]**	**p-value[c]**
Age						
< 45 years	0	(0.0, 24.7)	18 (51.4)	(34.0, 68.6)	51.4 (34.9, 68.0)	< 0.001
45 to 64 years	1 (4.3)	(0.1, 21.9)	24 (53.3)	(37.9, 68.3)	49.0 (32.2, 65.8)	
≥ 65 years	0	(0.0, 60.2)	4 (100.0)	(0.0, 60.2)	100.0 (100.0, 100.0)	
Sex						
Male	0	(0.0, 41.0)	10 (52.6)	(28.9, 75.6)	52.6 (30.2, 75.1)	< 0.001
Female	1 (3.0)	(0.1, 15.8)	36 (55.4)	(42.5, 67.7)	52.4 (38.9, 65.8)	
Active vitamin D dose						
Low dose	1 (33.3)	(0.8, 90.6)	5 (83.3)	(35.9, 99.6)	50.0 (-11.1, 100.0)	< 0.001
Medium dose	0	(0.0, 26.5)	11 (50.0)	(28.2, 71.8)	50.0 (29.1, 70.9)	
High dose	0	(0.0, 13.7)	30 (53.6)	(39.7, 67.0)	53.6 (40.5, 66.6)	
Calcium dose						
0-2000 mg/day	1 (3.4)	(0.1, 17.8)	35 (61.4)	(47.6, 74.0)	58.0 (43.7, 72.2)	< 0.001
> 2000 mg/day	0	(0.0, 28.5)	11 (40.7)	(22.4, 61.2)	40.7 (22.2, 59.3)	
Duration of Hypoparathyroidism						
≤ 5 years	1 (10.0)	(0.3, 44.5)	12 (80.0)	(51.9, 95.7)	70.0 (42.5, 97.5)	< 0.001
> 5 to 10 years	0	(0.0, 24.7)	17 (63.0)	(42.4, 80.6)	63.0 (44.7, 81.2)	
> 10 years	0	(0.0, 19.5)	17 (40.5)	(25.6, 56.7)	40.5 (25.6, 55.3)	
Region						
North America	1 (4.8)	(0.1, 23.8)	26 (60.5)	(44.4, 75.0)	55.7 (38.5, 72.9)	< 0.001
Western Europe	0	(0.0, 26.5)	13 (52.0)	(31.3, 72.2)	52.0 (32.4, 71.6)	
Hungary	0	(0.0, 41.0)	7 (43.8)	(19.8, 70.1)	43.8 (19.4, 68.1)	

CI = confidence interval; N = total number of subjects, n = number of subjects in each subgroup
Note: Percentages are based on the number of subjects in each treatment arm. For calcitriol: low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day; for alphacalcidol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day).
a. Based on exact 95% CI.
b. Treatment difference is calculated as the percentage of subjects meeting the primary endpoint in the Natpara group minus the percentage of subject meeting the primary endpoint in the placebo group; the 2-sided asymptotic 95% CI is based on normal approximation.
c. Based on Cochran-Mantel-Haenszel (CMH) general association test with adjustment for each subgroup factor.
d. The percentages represent the percent of subjects who met the three criteria in each of the age subgroup; hence column total will be greater than 100%.

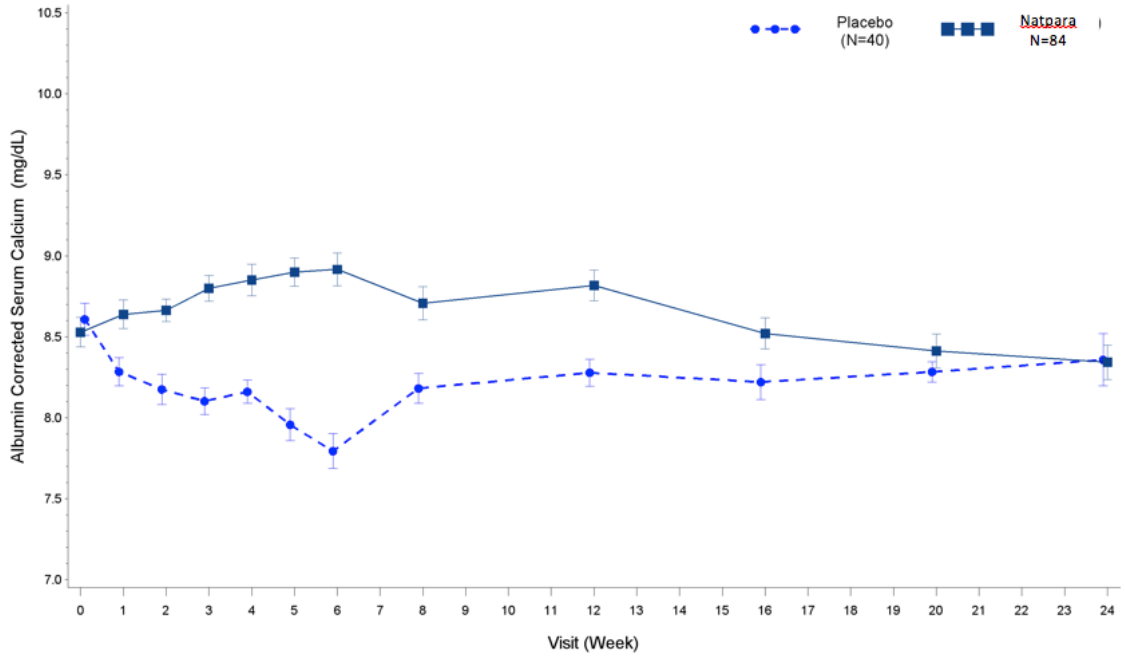
4.4.1 Triple Endpoint Based Upon Weeks 16, 20, and 24

In the Natpara group, 37 of 84 subjects (44.0%) met and maintained the primary endpoint criteria (based on investigator-prescribed data) over the last 3 treatment study visits (i.e., Weeks 16, 20, and 24) compared to 1 of 40 subjects (2.5%) in the placebo group ($p < 0.001$), consistent with a durable response. Findings were similar when analysis was based upon subject-recorded diary data, 42.9% compared to 2.5%, respectively ($p < 0.001$).

4.4.2 Serum Calcium over Time

At Week 1, mean albumin-corrected total serum calcium concentration increased in the Natpara group and decreased in the placebo group (Figure 19). The increase in the Natpara group corresponded with large reductions in doses of oral calcium and active vitamin D (starting at Week 2, Figure 20 and Figure 21) in the placebo group, mean serum calcium concentrations began to increase after Week 6, as oral calcium and active vitamin D increased towards baseline concentrations.

Figure 19. Mean (±SE) Albumin-corrected Total Serum Calcium – REPLACE



N = total number of subjects; SE = standard error
Note: Serum calcium target range = 8.0 to 9.0 mg/dL.

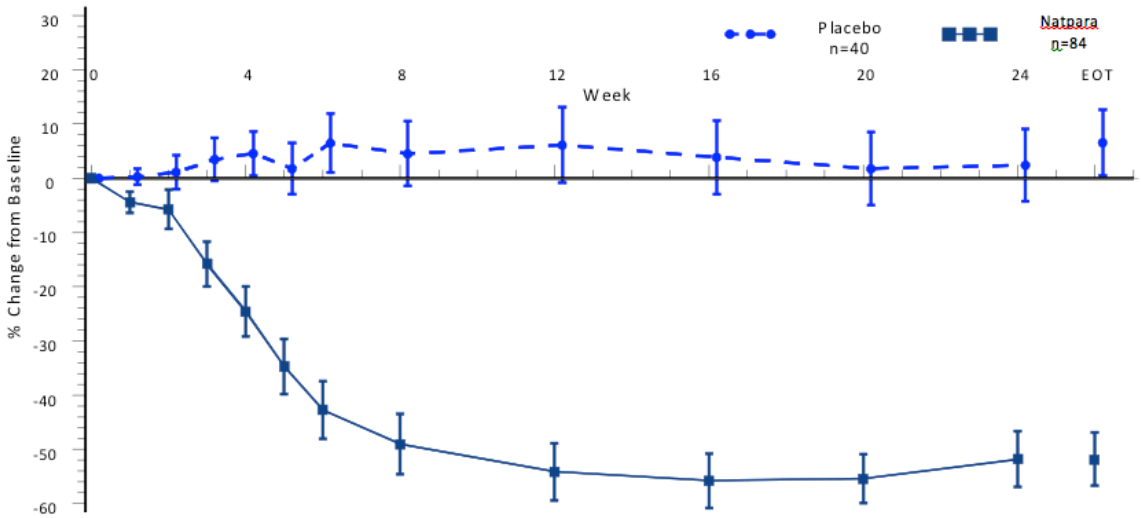
4.5 Findings for Secondary Endpoints

REPLACE had 3 ordered secondary endpoints: percentage change in oral calcium dose; active vitamin D independence with ≤ 500 mg/day of oral calcium; and frequency of hypocalcemia symptoms.

4.5.1 Percent Change in Calcium Dose

At Week 24, there was a 51.8% [± 45.7%] mean decrease from baseline in calcium dose in the Natpara group compared to a (2.4% [± 38.4%] mean increase in the placebo group (difference between groups $p < 0.001$) (Figure 20). Mean ± SD oral calcium dose was 2171 ± 1474 mg at baseline and 987 ± 1000 mg at Week 24 in the Natpara group and 1978 ± 926 mg at baseline and 1932 ± 977 mg at Week 24 in the placebo group.

Figure 20. Mean (±SE) of Percent Change from Baseline in Oral Calcium Dose Based on Investigator-prescribed Data – REPLACE

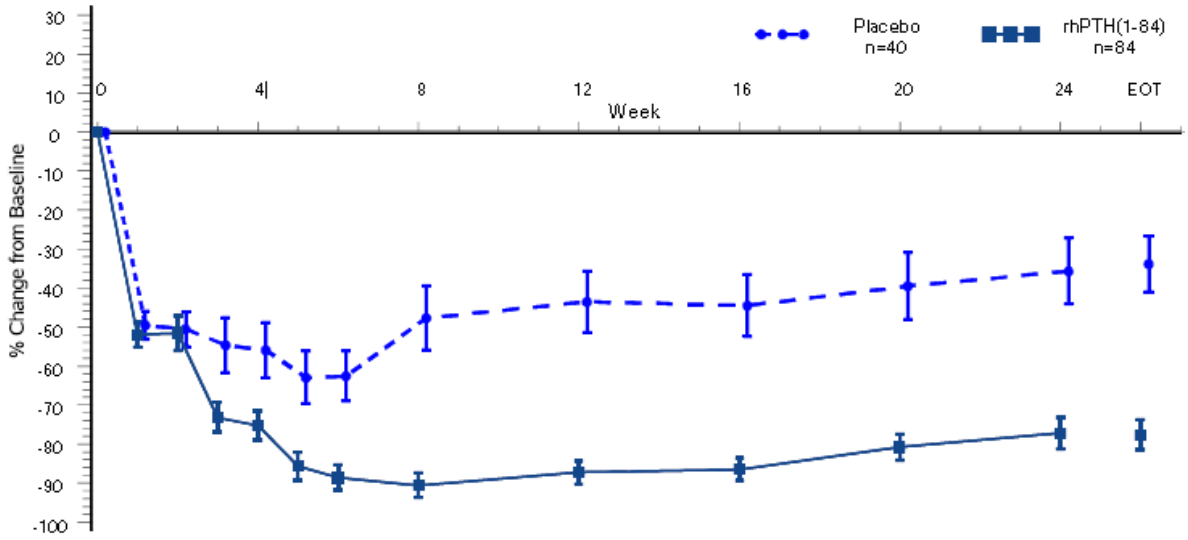


EOT = end of treatment (last observation during the treatment period); n = number of subjects; SE = standard error

4.5.2 Oral Active Vitamin D Independence

At Week 24, 35 of 84 subjects (41.7%) treated with Natpara were independent of vitamin D and were receiving no more than 500 mg of calcium compared with 1 subject (2.5%) in the placebo group ($p < 0.001$). Figure 21 shows the reductions made to daily active vitamin D dose over the course of the study. Mean ± SD oral active vitamin D dose was 0.89 ± 0.45 µg at baseline and 0.23 ± 0.37 µg at Week 24 in the Natpara group and 0.83 ± 0.40 µg at baseline and 0.54 ± 0.43 µg at Week 24 in the placebo group.

Figure 21. Mean (±SE) of Percent Change from Baseline in Active Vitamin D Based on Investigator-prescribed Data – REPLACE



EOT = end of treatment (last observation during the treatment period); n = number of subjects; SE = standard error

4.5.3 Hypocalcemia Symptom Rates

During Week 16 to 24, 29 of 84 subjects (34.5%) treated with Natpara exhibited 1 or more symptoms of hypocalcemia (defined in Section 4.1.2.2) compared to 15 of 40 subjects (37.5%) in the placebo group (OR = 0.879; 95% CI: 0.402 to 1.922; p = 0.747).

4.5.4 Prespecified Exploratory Endpoints

The exploratory endpoints were prespecified and evaluated the physiologic effects of PTH hormone replacement.

4.5.4.1 Serum Calcium Concentration and 24-Hour Urinary Calcium Excretion

Albumin-corrected total serum calcium concentration and 24-hour urinary calcium excretion over the course of the study are shown for the Natpara group in Figure 22 and for placebo in Figure 23. At screening, mean 24-hour urinary calcium excretion was 283 mg/24 hr and increased after optimization on oral calcium and vitamin D.

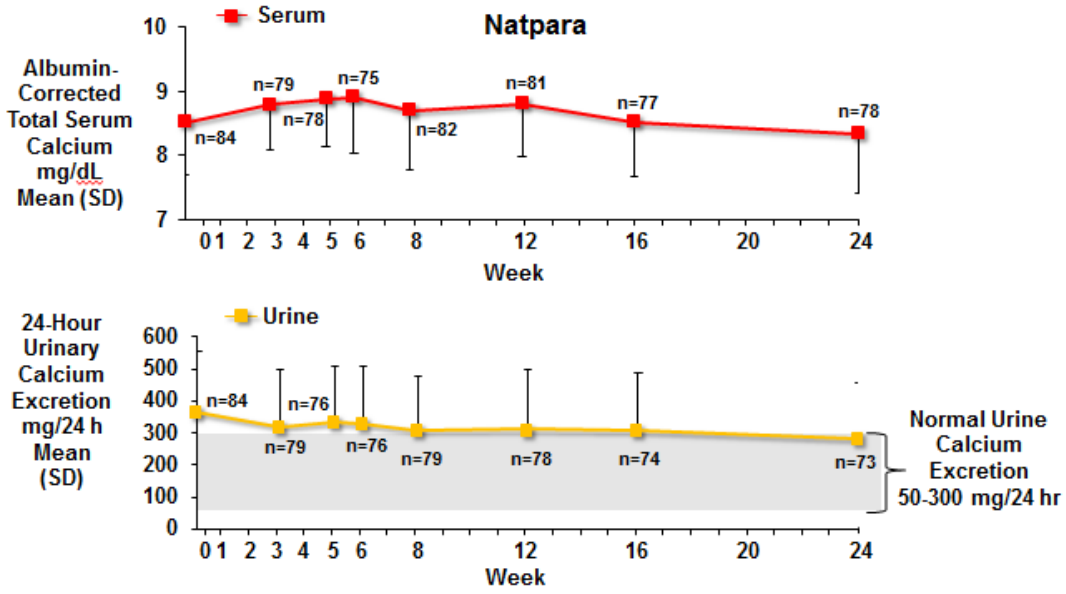
In the Natpara group, mean serum calcium concentration increased over the first 6 weeks of REPLACE, consistent with PTH activity, without a concomitant increase in urinary

calcium excretion. Over the course of the study, mean serum calcium concentration remained in the target range of 8.0 to 9.0 mg/dL (mean ± SD, 8.5 ± 0.8 mg/dL at baseline and 8.3 ± 0.9 mg/dL at Week 24) while mean 24-hour urine calcium excretion decreased into the normal reference range (mean ± SD, 361.1 ± 193.9 mg/24 hr at baseline and 276.9 ± 177.9 mg/24 hr at Week 24) among subjects who completed treatment. In the placebo group, mean 24-hour urinary calcium excretion decreased over the first 6 weeks of REPLACE as a consequence of a mean decrease in serum calcium concentration which corresponded to withdrawal of active vitamin D and oral calcium during that time period. Increased usage of oral calcium and vitamin D after Week 6 led to mean increases in both serum calcium concentration (mean ± SD, 7.8 ± 0.6 mg/dL at Week 6 and 8.4 ± 0.9 mg/dL at Week 24) and 24-hour urinary calcium excretion (mean ± SD, 210.7 ± 157.4 mg/24 hr at Week 6 and 243.7 ± 140.8 mg/24 hr at Week 24) among subjects who completed treatment. These findings support the need for PTH to maintain the balance of serum and urinary calcium homeostasis.

At baseline, approximately half of subjects in both treatment groups had 24-hour urine calcium excretion > 300 mg/24 hr (57% [42/74] and 48% [16/33] of subjects in the Natpara and placebo groups, respectively). At Week 24, a lower percentage of subjects in the Natpara group (34%, 25/74) as compared to the placebo group (39%, 13/33) had 24-hour urine calcium excretion > 300 mg/24 hr; p = 0.293, supporting the role of PTH to reduce the rate of hypercalciuria. Results of shift analyses (i.e., from normal to out of the reference range, and vice versa) are presented in Section 6.4.3.1.2.

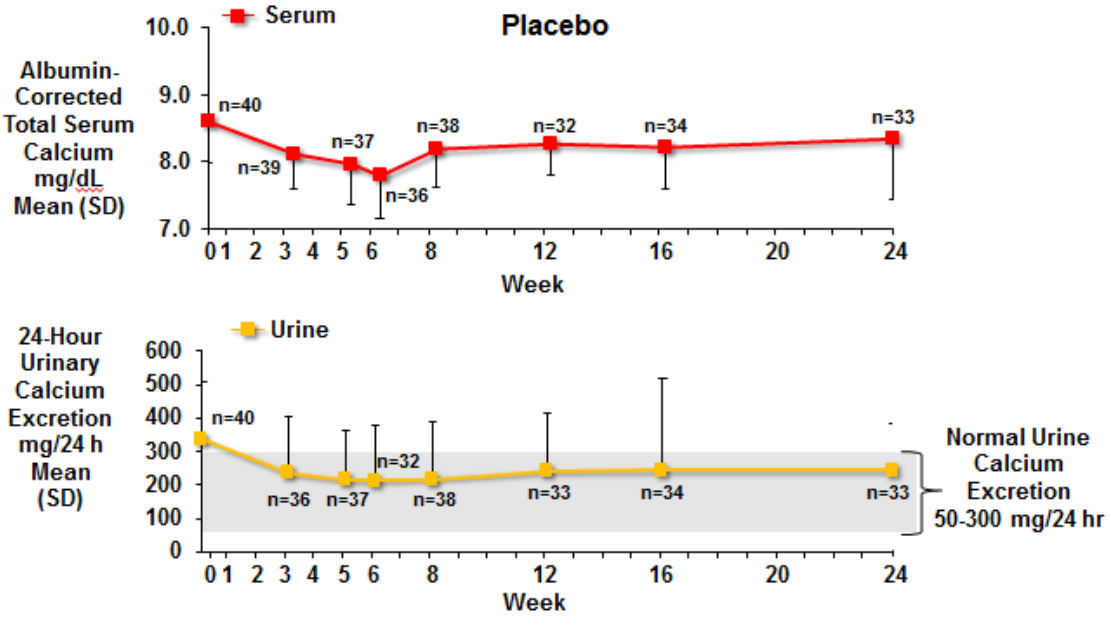
The time course of these changes suggests that Natpara treatment led to greater urinary calcium reabsorption, allowing serum calcium to rise within the normal range despite significant decreases in doses of oral calcium and active vitamin D.

Figure 22. Mean (± SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion – Natpara – REPLACE



SD = standard deviation
Serum calcium target range of 8.0 to 9.0 mg/dL
Normal urine calcium excretion 50-300 mg/24 hr

Figure 23. Mean (±SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion – Placebo – REPLACE

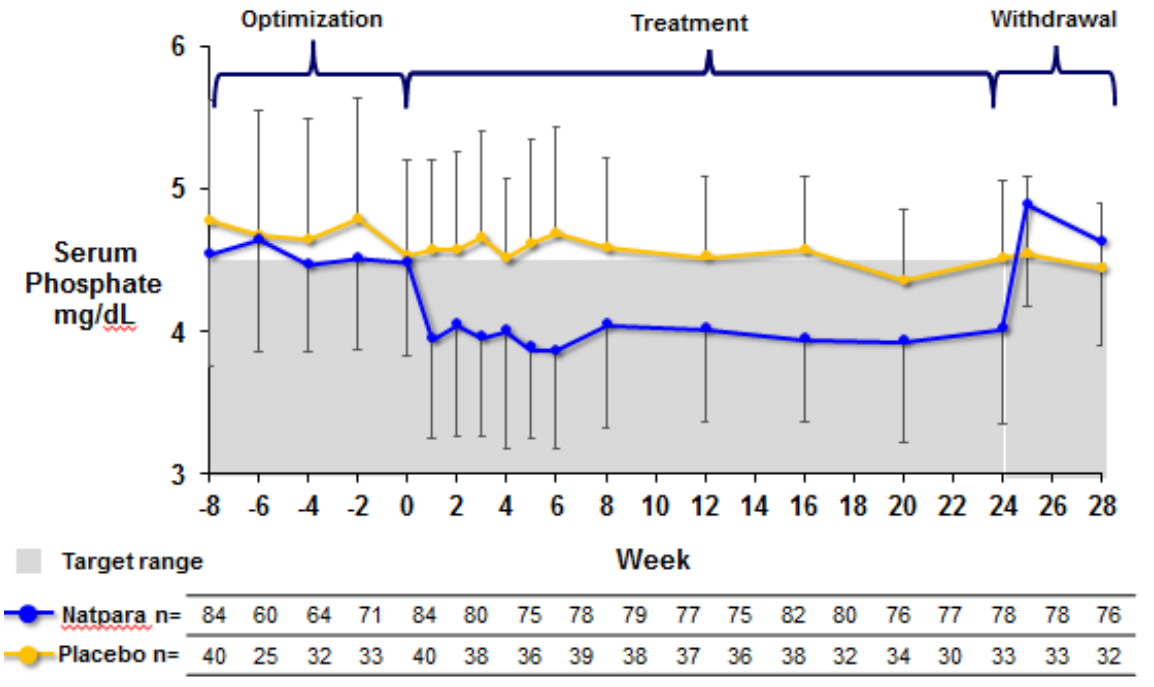


ITT = Intent-to-Treat; n = number; SD = standard deviation
Note: Normal urine calcium excretion is 50-300 mg/24 hr.

4.5.4.2 Serum Phosphate

Screening and baseline concentrations of serum phosphate were at or above the upper limit of the reference range in both treatment groups. Mean serum phosphate concentration decreased substantially in the Natpara group, beginning at Week 1 and remained at this lower concentration throughout the remainder of the study. In contrast, in the placebo arm, the mean serum phosphate concentration remained at or close to the baseline concentration at all time points throughout the treatment portion of the study (Figure 24). Natpara-treated subjects experienced significant reduction in serum phosphate concentrations from baseline to Week 24 ($p < 0.001$). Among the subjects who completed treatment, serum phosphate concentrations were significantly decreased from 4.49 (± 0.66) mg/dL to 4.03 (± 0.67) mg/dL in the Natpara group and remained unchanged in the placebo group (4.53 [± 0.66] to 4.53 [±0.52] mg/dL), showing the reduction of hyperphosphatemia with PTH treatment. It is interesting to note that following the withdrawal of Natpara, the mean serum phosphate levels dramatically increased above the upper limit of normal and above baseline levels at approximately 1 week post-treatment, due to a return of subjects to their pretreatment oral calcium and active vitamin D regimens. Following this, the levels began to decrease somewhat, however did not return to baseline levels by the end of the 4-week withdrawal period.

Figure 24. Mean (±SE) of Change from Baseline in Serum Phosphate – REPLACE



n = total number of subjects in each treatment arm; SE = standard error
Note: The number of subjects in the withdrawal period are subjects who completed study

4.5.4.3 Calcium-Phosphate Product

In the Natpara group, the mean calcium-phosphate product decreased significantly ($p < 0.001$) from baseline to Week 24 (from 39.8 [± 6.7] to 34.8 [±5.73] mg^2/dL^2; LS Mean = -5.2;), compared to no change in the placebo group (40.8 [± 6.5] and 39.9 [±5.3] mg^2/dL^2 at the respective visits, LS mean=-0.45).

An analysis was conducted to assess the proportion of subjects who had a calcium-phosphate product > 55 mg^2/dL^2, a level at which increased risk of calcium-phosphate crystal deposition may occur. At baseline, 1 subject in the Natpara group and no subjects in the placebo group had a calcium-phosphate product that was > 55 mg^2/dL^2. At Week 4, 2 subjects in the Natpara group had a calcium-phosphate product above 55 mg^2/dL^2. From Week 5 on, no subject in either treatment group had a calcium-phosphate product above 55 mg^2/dL^2 until Week 24 when a high calcium-phosphate product was reported in 1 subject in the placebo group.

4.5.4.4 Bone Turnover Biomarkers

As is expected in subjects with long-standing hypoparathyroidism, bone metabolism was low at baseline in REPLACE, as reflected in low-normal bone turnover markers concentrations.

Over the course of the 24-week study, Natpara increased bone formation as evidenced by mean increases in:

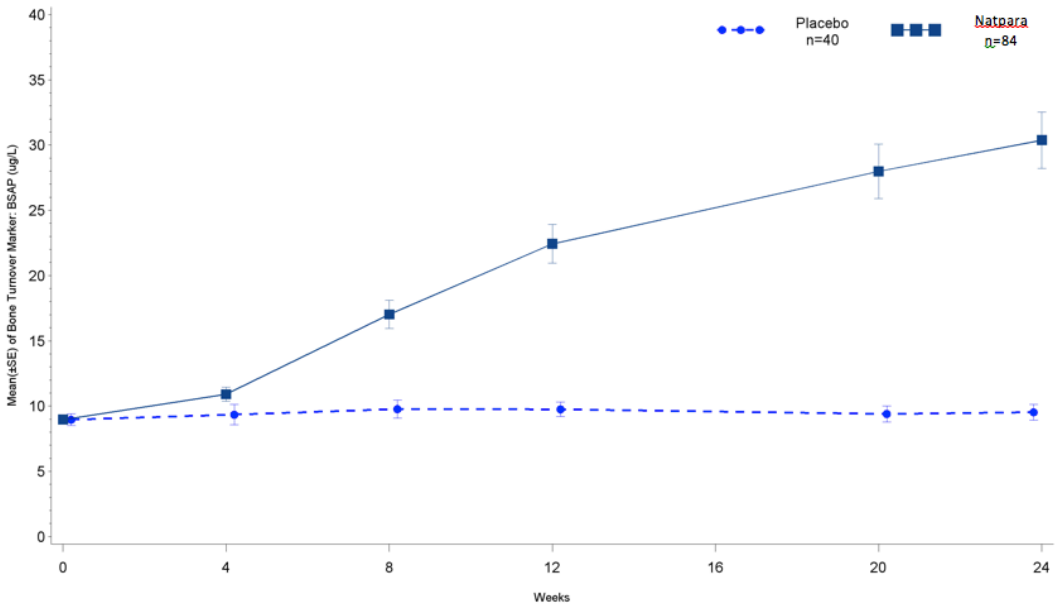
- bone-specific alkaline phosphatase (BSAP) – Figure 25
- procollagen type 1 amino-terminal propeptide [P1NP] – Figure 26, and
- osteocalcin – Figure 27

Natpara also favorably affected bone resorption as evidenced by a mean increase in:

- carboxy-terminal telopeptide of type I collagen [s-CTx] – Figure 28

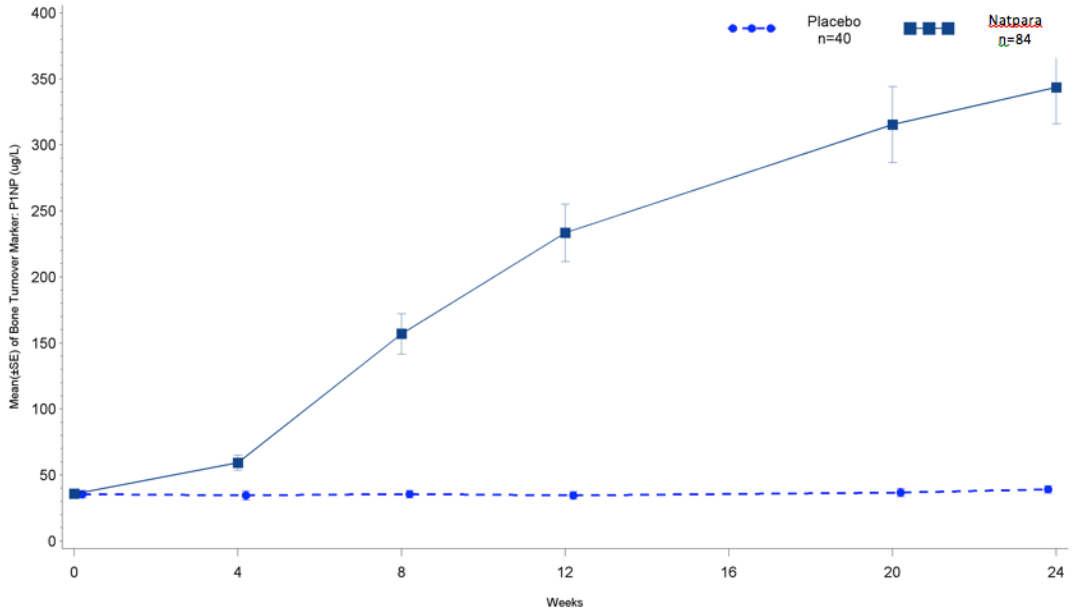
In contrast, bone markers did not change in the placebo group ($p < 0.001$ vs. Natpara for all markers at Week 24).

Figure 25. Mean (±SE) of Change from Baseline in BSAP – REPLACE



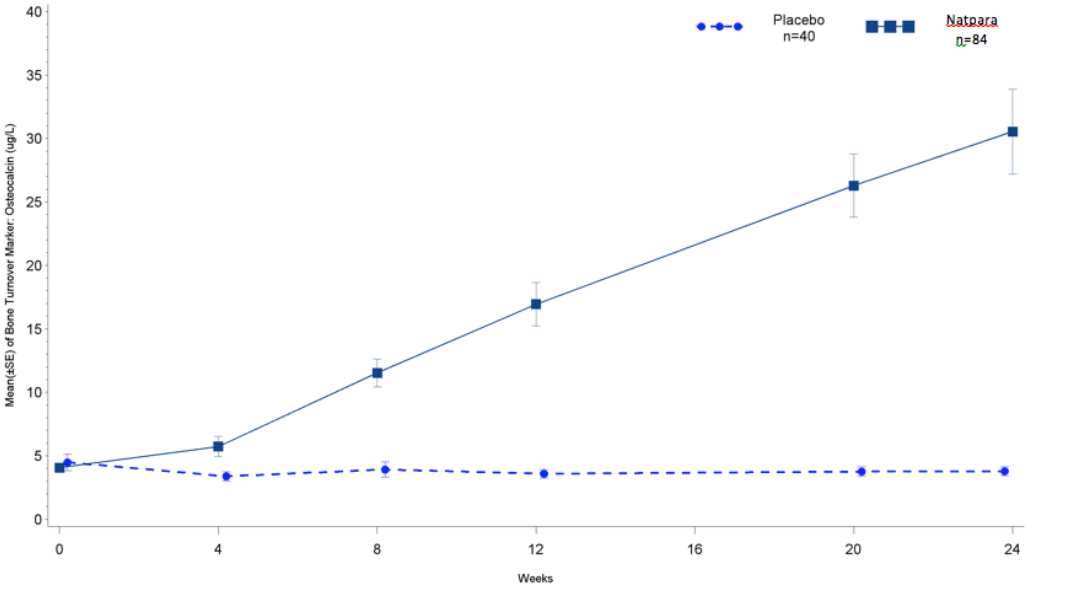
BSAP = bone-specific alkaline phosphatase; n = number; SE = standard error
Normal range: Males, 6 - 30 µg/L; Females, 3 - 19 µg/L (premenopausal), 6 - 26 µg/L (postmenopausal)

Figure 26. Mean (±SE) of Change from Baseline in P1NP – REPLACE



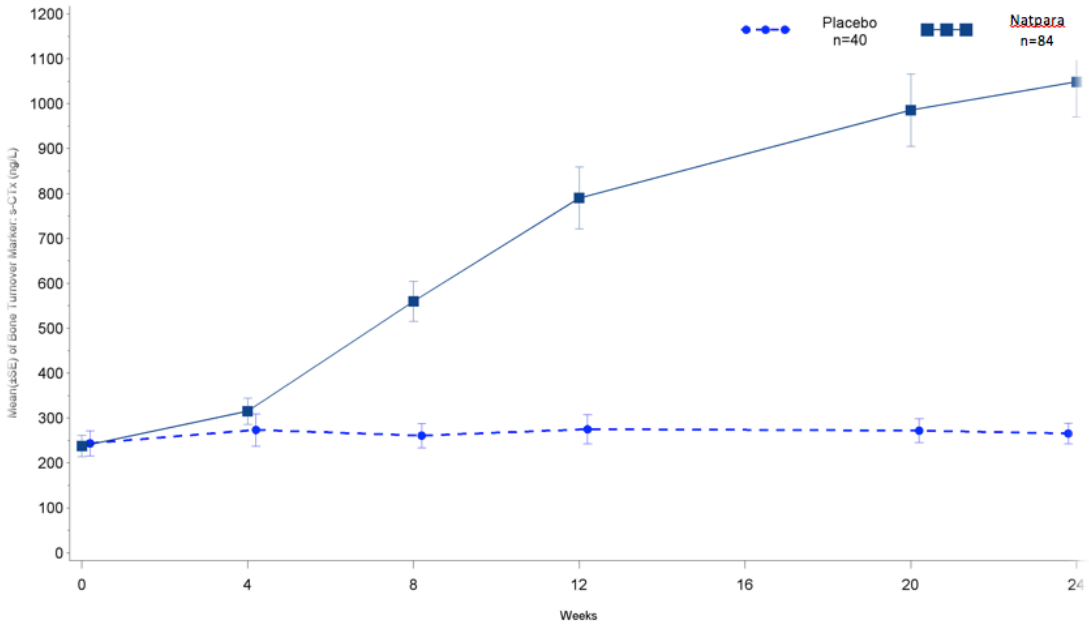
n = number; P1NP = procollagen amino-terminal peptide; SE = standard error
Normal range: males and females, < 75 ng/mL

Figure 27. Mean (±SE) of Change from Baseline in Osteocalcin – REPLACE



n = number; SE = standard error
Normal range: males and females, < 2.0 – 22.0 ng/mL

Figure 28. Mean (±SE) of Change from Baseline in s-CTx – REPLACE



n = number; s-CTx = serum carboxy-terminal telopeptide of type I collagen; SE = standard error
Normal range: males 0.016 - 0.584 ng/mL (age 30-49), 0 - 0.704 ng/mL (age 50-69), 0 - 0.854 (age >70); females, 0.025 - 0.573 ng/mL (premenopausal), 0.104 - 1.008 ng/mL (postmenopausal)

4.5.4.5 Bone Mineral Density

Subjects underwent a dual energy x-ray absorptiometry (DXA) assessment at screening and at the end of treatment. BMD was expressed as direct measurements and Z-scores.

A Z-score is the comparison of a person's bone density with that of an average person of the same age, sex, and ethnicity. Baseline Z-scores were summarized into three categories: Z<-1, between -1 and 1, and >1., Overall baseline Z-scores indicated that participating study subjects had a high rate of increased bone density with 27.4% to 65.3% of subjects having Z-scores > 1 in each of the 7 scan locations scanned and 50% of the subjects had Z-scores >1 in 4 of the 7 locations.

At Week 24, there was a decrease towards normal in Z-scores in the Natpara group at all scan locations compared to a worsening of Z-scores in the placebo group. The mean changes from baseline to Week 24 in 5 of the 7 locations, hip-trochanter, hip-intertrochanter, hip-Ward's triangle , hip-femoral neck , were significantly better (lower) ($p < 0.05$) in the Natpara group compared to the placebo group Lumbar spine (L1-L4) and distal one‑third radius locations also showed a numerical improvement over placebo that did not reach the level of statistical significance.

The changes in direct BMD measurements mirrored those of the Z-scores. After treatment with Natpara, there were decreases towards normal from baseline in all hip locations. There were also improvements in lumbar spine and distal one-third radius, however, these changes were not significantly significant.

4.5.4.6 Quality of Life

In general, SF-36 domain scores in both of the treatment groups improved from baseline (after optimization of oral calcium and active vitamin D) to Week 24. While there were no statistically significant between-group differences for any of the individual domains, there was a significant reduction among the Natpara-treated subjects in bodily pain ($p = 0.014$) and there were significant improvements in the role physical ($p = 0.033$), vitality ($p < 0.001$), general health ($p = 0.002$), and mental health ($p = 0.016$) domains (Table 22). There were no significantly better within-group scores in the placebo group.

Definitive improvement in QoL was not observed in REPLACE likely due to the study design that focused on serum calcium concentration and by the limitation in up-titration after Week 8.

Table 22. Mean Change from Baseline at Week 24 in the Short-Form 36 – REPLACE

	Placebo				Natpara				Between Group Comparison[b]		
Short Form-36 Domain	Baseline Mean	Week 24 Mean	Mean Change from Baseline	p-value[a]	Baseline Mean	Week 24 Mean	Mean Change from Baseline	p-value[a]	LS-Mean Difference	95% CI	p-value
Physical Functioning	71.3	72.0	3.57	0.2630	78.0	80.7	2.32	0.2466	1.11	(-5.93, 8.14)	0.7560
Role-Physical	72.5	71.8	1.89	0.6236	74.2	79.6	5.32	0.0327	5.05	(-2.87, 12.98)	0.2090
Bodily Pain	68.0	65.0	-0.45	0.9009	66.6	72.5	6.21	0.0142	6.83	(-1.45, 15.11)	0.1047
General Health	60.1	58.1	0.61	0.8141	57.5	62.4	4.93	0.0016	4.26	(-1.07, 9.59)	0.1161
Vitality	52.5	57.0	4.73	0.0945	55.4	63.6	7.43	0.0009	4.16	(-2.17, 10.49)	0.1949
Social Functioning	76.9	78.0	1.14	0.7503	78.5	81.8	2.80	0.2511	2.35	(-5.43, 10.14)	0.5502
Role-Emotional	80.0	82.8	4.55	0.2008	83.7	85.2	0.99	0.6443	-1.2	(-8.07, 5.63)	0.7252
Mental Health	72.5	73.3	2.27	0.3248	74.3	78.9	3.82	0.0157	2.48	(-2.68, 7.64)	0.3428
Physical Component Scores	45.7	44.7	0.28	0.8007	46.1	48.1	2.10	0.0038	2.09	(-0.38, 4.56)	0.0965
Mental Component Scores	48.1	49.7	1.81	0.1499	49.2	51.4	1.67	0.0690	0.35	(-2.50, 3.20)	0.8065

ANCOVA = analysis of covariance; CI = confidence interval; LS = least square

Note: The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The higher the score the less disability.

a. Paired t-test was used to assess the within group difference between baseline and Week 24.

b. Based on ANCOVA model with actual change as the dependent variable and the treatment as the factor and baseline value as the covariate.

4.6 REPLACE - Efficacy Conclusions

The superiority of Natpara on the primary efficacy endpoint noted above shows that Natpara treatment is able to maintain serum calcium levels while significantly reducing oral calcium and active vitamin D requirements. These effects were not seen in the placebo group. Two of the 3 secondary endpoints showed statistically better results compared to placebo. The other secondary endpoint failed to show superiority to optimized current calcium therapy in reducing symptoms of hypocalcemia. Additionally, the exploratory endpoints demonstrate the underlying physiologic benefits of PTH to reduce hypercalciuria, reduce hyperphosphatemia, and increase BTMs. The primary endpoint, supported by the secondary and exploratory endpoints, provides a constellation of positive evidence that demonstrates the effectiveness of Natpara as a hormone replacement for the treatment of hypoparathyroidism.

5 Efficacy Findings in RACE

5.1 Study Methodology

RACE complements the findings in REPLACE and evaluates longer-term treatment with Natpara in patients with hypoparathyroidism. RACE is an ongoing, open-label study in the US evaluating the long-term safety and tolerability of Natpara for the treatment of adult male and female subjects with hypoparathyroidism. RACE also provides opportunity to assess longer-term efficacy. Subjects must have previously completed REPLACE (after completing the 24-week treatment period and the 4-week follow-up withdrawal period) and/or RELAY (8 weeks of active therapy) (Figure 16). Treatment with Natpara was not continuous for patients transitioning from the end of REPLACE and entering into RACE.

A total of 53 subjects enrolled in RACE from 1 or both of the 2 previous studies. The site excluded from the REPLACE study also participated in RACE which led to the exclusion of data from 4 subjects from RACE who were enrolled at that site. Therefore, data is presented on 49 Natpara subjects in this study.

Natpara was titrated in the range of 25 µg SC QD to 100 µg SC QD. Adjustment of calcium and active vitamin D regimens was based on total serum calcium concentrations, with the goal of reducing or removing active vitamin D treatment to the maximum degree clinically possible and decreasing the prescribed oral calcium to ≤ 500 mg daily.

The starting dose of Natpara was 50 µg SC QD for subjects with a total serum calcium value of ≤ 9.5 mg/dL. Subjects with a total serum calcium value of > 9.5 mg/dL had a starting dose as follows:

- Subjects treated with calcium (≥ 500 mg) and/or any active vitamin D had the doses of each reduced or stopped and started Natpara treatment at a dose of 50 µg SC QD.
- Subjects treated with minimal or no calcium (< 500 mg) and no active vitamin D had a starting Natpara dose of 25 µg SC QD.

At any time during the study, dose titration up or down was permitted in increments of 25 µg to a maximum dose of 100 µg daily and a minimum dose of 25 µg daily, with the goal of achieving or maintaining total serum calcium concentrations in the range of 8.0 to 9.0 mg/dL.

Study visits during the first 12 months of the study were conducted at Weeks 1 (baseline), 4, 8, and then every 8 weeks thereafter up to Week 48. A Week 52 visit was scheduled 4 weeks later. At the end of Week 52, subjects were invited to extend their study drug regimen. During this time, subjects returned to the clinic for interim visits every 2 months (e.g., Months 14, 16, 18).

5.2 Subject Disposition and Baseline Characteristics

As of the interim data cutoff for RACE, 49 subjects were enrolled at 12 US sites, 47 (96%) of whom had at least 52 weeks of continuous treatment and 40 had at least 104 weeks of continuous treatment, showing good persistence on Natpara treatment.

At baseline, the mean age of 49 subjects in RACE was 48.1 (± 9.78) years. The study population was primarily female (40/49, 81.6%) and the majority were white (46/49, 93.9%) and 1 Hispanic or Latino (1/49, 2.0%). Mean body mass index (BMI) was 31.5 (± 7.16) kg/m^2. More than a third of subjects (20-/49, 40.8%) were on a calcitriol dose greater than 0.5 µg/day; and more than a third (18/49, 36.7%) were on calcium dose > 2000 mg/day. The mean duration of hypoparathyroidism was 15.9 (±12.49) years.

5.3 Study Drug Dose

The overall mean duration of treatment in RACE was 106.8 weeks. Table 23 shows the study drug dose level at the time of interim data cut-off. The investigator initiated treatment at 50 µg QD for 46 of the 49 study subjects, at 25 µg QD for 2 subjects, and at 100 µg QD for 1 subject.

Thirty-three of the 49 study subjects (67.3%) underwent incremental dose titration to 100 µg SC QD and remained at that dose until the time of the interim data cut-off. None of the subjects was at a 25 µg SC QD dose level at the time of interim data cut-off.

Table 23. Daily Dose Level as of 30 September 2013 – RACE

Dose Level	Natpara = 49 n (%)
25 µg	0 (0)
50 µg	10 (20.4)
75 µg	6 (12.2)
100 µg	33 (67.3)

N = total number of subjects; n = number of subjects at each dose level

5.4 Efficacy Findings

Baseline was either the beginning of REPLACE for subjects treated with Natpara or the beginning of RELAY for subjects who received placebo in REPLACE.

Efficacy Endpoints

Although the RACE study was uncontrolled and not designed to directly assess efficacy, the triple endpoint from REPLACE was analyzed for completeness. Of the 39 subjects who had valid data and who received Natpara for 104 weeks in RACE, 24 (62%) met the triple endpoint (as defined in REPLACE) at Week 24, 25 (64%) at Week 52, and 19 (49%) at Week 104 (Table 24).

Table 24. Analysis of Key Endpoints Based on Investigator-prescribed Data – ITT Population – RACE

Endpoint	Baseline N = 39	Week 24 N = 39	Week 52 N = 39	Week 104 N = 39
Met endpoint, n (%)	NA	24 (61.5%)	25 (64.1%)	19 (48.7%)
% Reduction in oral calcium dose	NA	66%	61%	53%
% Reduction in oral active vitamin D dose	NA	71%	71%	71%
Albumin-corrected serum calcium, mean (SD)	8.4 (0.7)	8.3 (0.6)	8.5 (0.6)	8.3 (0.7)

NA = not available.

Subjects who met the primary endpoint had: a ≥ 50% reduction from baseline or ≤ 500 mg of daily calcium; 2) a ≥ 50% reduction from baseline or ≤ 0.25 µg of daily calcitriol; and, 3) an albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline (≥ 7.5 mg/dL) and did not exceed the upper limit of normal.

5.4.1 Maintenance of Effect

Results from the RACE study demonstrated a consistency of Natpara effect over time. At 24, 52 and 104 weeks physiological effects were maintained, including calcium-phosphate product, serum phosphate, and urinary calcium, while sustaining stable serum calcium (Table 25). Effects of Natpara on bone formation and resorption were seen by the normalization of BTMs of BSAP and CTX (Figure 29). After 104 weeks on Natpara, BMD remained unchanged from baseline, indicating maintenance of the benefit realized in the previous studies (Table 26).

5.4.2 Serum Calcium, Serum Phosphate, Calcium-Phosphate Product, and 24-hour Urinary Calcium Excretion

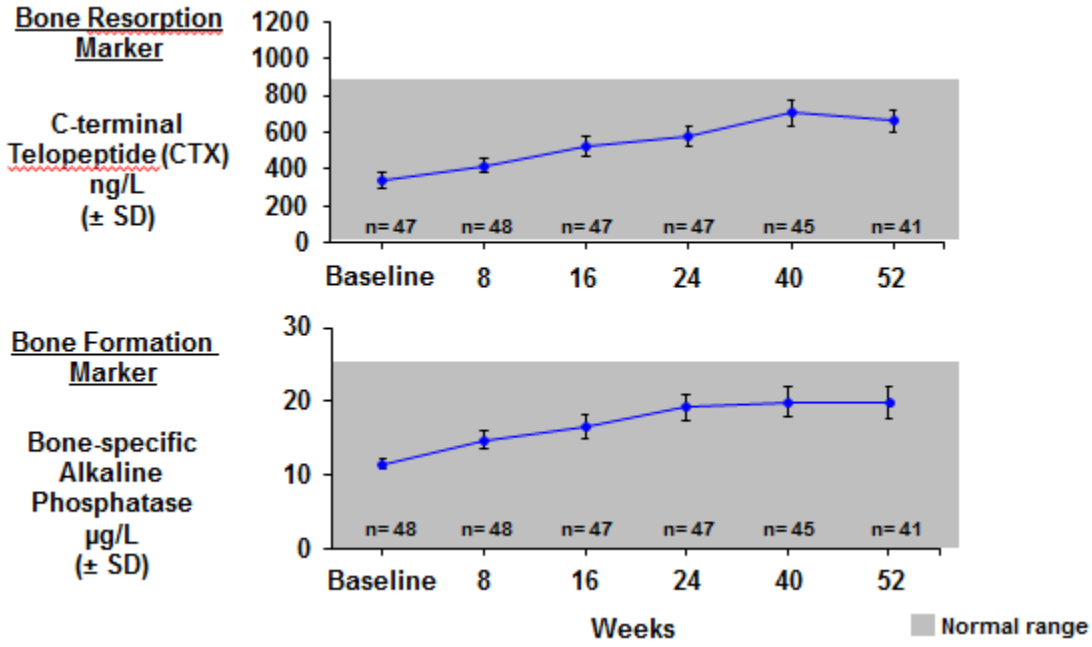
Table 25. Maintenance of Physiological Effects of Natpara – RACE

Natpara Parameter, mean (SD)	Baseline (n=49)	Week 24 (n=47)	Week 52 (n=46)	Week 104 (n=39)
Albumin-corrected Serum Calcium mg/dL	8.4 (0.7)	8.4 (0.6)	8.4 (0.6)	8.3 (0.7)
Calcium-Phosphate Product mg^2/dL^2	43 (6.5)	35 (5.9)	36 (4.9)	35 (8.8)
Serum Phosphate mg/dL	4.8 (0.6)	4.0 (0.7)	4.1 (0.7)	4.2 (0.8)
24-h Urine Calcium Excretion mg/24 hours	357 (200)	-	328 (175)	281 (170)

n = total number of subjects at time point indicated; SD = standard deviation

5.4.3 Bone Turnover Markers and Bone Mineral Density

Figure 29. Persistence of Effect in Bone Turnover Markers – RACE



n = number of subjects with at least 1 valid value; SD = standard deviation
Note: Number of subjects at baseline refers to the baseline of RACE.

Table 26. Persistence of Effects in Bone Mineral Density – RACE

Bone Mineral Density (g/cm2) Location	Statistic	Baseline (N = 49)	Week 104 (N = 38)	Change from Baseline
Lumbar spine (L1-L4)	n	45	38	34
	Mean	1.27	1.29	0.01
	(SD)	(0.19)	(0.19)	(0.10)
Hip (total)	n	44	36	32
	Mean	1.12	1.11	-0.12
	(SD)	(0.16)	(0.16)	(0.06)
Distal one-third radius	n	45	37	33
	Mean	0.79	0.78	-0.02
	(SD)	(0.11)	(0.12)	(0.06)

N = total number of subjects; n = number of subjects at time point indicated

The findings in RACE are consistent with continued PTH activity with Natpara, supporting the long-term treatment of hypoparathyroidism.

6 SAFETY EXPERIENCE WITH NATPARA

Across the hypoparathyroidism and osteoporosis development programs, 3344 unique subjects were exposed to at least 1 dose of Natpara.

Section 6.1 reviews the experience in the 361 subjects treated with Natpara in the hypoparathyroidism program. Section 6.2 reviews the experience in 2864 subjects in the osteoporosis program who were all treated with 100 µg/day. The postmarketing experience is reviewed in Section 6.3. Section 6.4 reviews hypocalcemia, hypercalcemia, hypercalciuria, events reported with the pen device, immunogenicity and osteosarcoma in more detail.

6.1 Hypoparathyroidism Development Program

6.1.1 Extent of Exposure

Overall, 482 unique subjects were treated with at least 1 dose of Natpara in the hypoparathyroidism development program, with 361 treated in the pharmacology studies and 121 subjects treated in efficacy and safety clinical studies.

In the efficacy and safety studies, 108 (of 121) subjects were treated for at least 24 weeks and 47 were treated for at least 52 weeks, with a mean cumulative duration of treatment of 67.6 weeks. The maximum exposure to Natpara across these studies was 162.6 weeks (Table 27) and there were 156.77 person-years of treatment (Table 28). In REPLACE and RACE, 56.0% and 67.3% of subjects, respectively, had a final dose of 100 µg.

Table 27. Exposure to Natpara - Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

Exposure Parameter	Natpara (Any dose) N=121
Duration of exposure, n (%)	
< 1 week	0
1 - < 12 weeks	5 (4.1)
12 - < 24 weeks	8 (6.6)
24 - < 52 weeks	61 (50.4)
52 - < 104 weeks	3 (2.5)
104 - < 156 weeks	39 (32.2)
≥ 56 weeks	5 (4.1)
Cumulative exposure, n (%)	
Any exposure	121 (100)
≥ 1 week	121 (100)
≥ 12 weeks	116 (95.9)
≥ 24 weeks	108 (89.3)
≥ 52 weeks	47 (38.8)
≥ 104 weeks	44 (36.4)
≥ 156 weeks	5 (4.1)
Exposure duration (weeks)	
n	121
Mean	67.60
SD	52.024
Median	48.00
Min, Max	5.3, 162.6
Person-years of exposure	156.77

Max = maximum; Min = minimum; N = number of subjects in the treatment group; n = number of subjects with specified exposure in the treatment group; SD = standard deviation
Notes: Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. RACE is currently ongoing. The exposure for ongoing subjects is calculated up to the date of data cutoff.

Table 28. Exposure to Natpara by Study - Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

	REPLACE		RELAY		RACE	REPEAT	Total Efficacy and Safety Studies
Exposure Parameter	**Placebo N = 40**	**Natpara (50/75/100 µg) N = 84**	**Natpara (25 µg) N = 19**	**Natpara (50 µg) N = 23**	**Natpara (25/50/75/100 µg) N = 49**	**Natpara (50/75/100 µg) N = 24**	**Natpara (Any dose) N = 121**
Person-Years of Exposure	17.22	38.77	2.92	3.65	100.31	11.13	156.77
Final Dosage Level in the Treatment Period, n (%)							
25 µg		0			0	0	
50 µg		15 (17.9)			10 (20.4)	4 (16.7)	
75 µg		22 (26.2)			6 (12.2)	5 (20.8)	
100 µg		47 (56.0)			33 (67.3)	15 (62.5)	

Max = maximum; Min = minimum; N = number of subjects in the treatment group; n = number of subjects with specified exposure in the treatment group; SD = standard deviation

Note: RACE is currently ongoing. The exposure for ongoing subjects is calculated up to the date of interim data cutoff.

Notes: Final dosage level is only applicable to subjects on Natpara from studies REPLACE, RACE, and REPEAT. Each individual study column represents subjects' exposure within the respective study whereas the "Total NPS Sponsored Studies" column represents subjects' cumulative exposure across multiple studies. Therefore, exposure for a particular row within the total column differs from the sum of the exposure for the individual study columns.

6.1.2 Demographics and Baseline Characteristics

In the Efficacy and Safety studies in Hypoparathyroidism, mean age was about 50 years and most subjects were female and white (Table 29). The majority of subjects were treated with Natpara in North America.

Table 29. Demographics and Other Baseline Characteristics - Safety Population, Clinical Pharmacology and Efficacy and Safety Studies in Hypoparathyroidism

	Clinical Pharmacology Studies[a]	Efficacy and Safety Studies in Hypoparathyroidism[b]
Parameter	**Natpara (Any dose) N=359[c]**	**Natpara (Any dose) N=121**
Age at Screening (years)[d]		
Mean (SD)	50.0 (14.68)	47.4 (11.84)
Min, Max	18, 82	19, 74
Sex, n (%)		
Female	255 (71.0)	96 (79.3)
Male	104 (29.0)	25 (20.7)
Race, n (%)		
White	253 (70.5)	115 (95.0)
Black	46 (12.8)	1 (0.8)
Asian	0	2 (1.7)
Native Hawaiian/ Pacific Islander	0	2 (1.7)
Other	60 (16.7)	1 (0.8)
BMI (kg/m^2)		
Mean (SD)	26.03 (3.992)	29.94 (6.597)
Min, Max	18.0, 43.0	18.9, 49.6
Geographic Region of Enrollment, n (%)		
North America	226 (63.0)	72 (59.5)
Western Europe	133 (37.0)	25 (20.7)
Hungary	0	24 (19.8)

BMI = body mass index; Max = maximum; Min = minimum; N = number of subjects in the treatment group; n = number of subjects with non-missing baseline information; PD = pharmacodynamic; PK = pharmacokinetic; SD = standard deviation

Note: If a subject participated in more than one study, the demographic and baseline information from the first participated study for the integrated analysis group will be presented.

a. Clinical Pharmacology Studies include: PAR-C10-005, CL1-11-007, CL1-11-012, CL1-11-013, CL1-11-017, SH-PTH-0001, PBR 930811, PBR 930812, C09-002, Mosekilde IIT PK/PD Substudy, CL1-11-009, and CL1-11-010.

b. Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT.

c. Excluding 2 subjects who received the zinc chloride investigational formulation of Natpara

d.. Age reflects the subject's age at the first screening leading to enrollment.

6.1.3 Overall Safety Experience

Across the clinical studies in hypoparathyroidism, most patients reported at least 1 TEAE (Table 30). Lower incidence of events was observed in the clinical pharmacology studies, as they were shorter in duration.

The frequency of treatment-emergent serious adverse events (TESAEs) and TEAEs leading to discontinuation of Natpara among Natpara subjects was low across all experience and there were no deaths reported.

In REPLACE, subjects treated with Natpara had greater incidence of severe TEAEs and AEs leading to discontinuation, as compared to placebo subjects (Table 31). These events are discussed in more detail in subsequent sections.

Table 30. Overall Summary of On-treatment Treatment-emergent Adverse Events and Deaths - Safety Population – Clinical Pharmacology and Efficacy and Safety Studies in Hypoparathyroidism

	Clinical Pharmacology Studies[a]	Efficacy and Safety Studies in Hypoparathyroidism[b]
Parameter	Natpara (Any dose) N=359[c] n (%) E	Natpara (Any dose) N=121 n (%) E
Any TEAE	141 (39.3) 319	114 (94.2) 1416
TEAE by Highest Severity		
Mild	97 (27.0)	30 (24.8)
Moderate	41 (11.4)	60 (49.6)
Severe	3 (0.8)	24 (19.8)
Any TESAE	1 (0.3) 1	10 (8.3) 17
TESAE by Highest Severity		
Mild	0	0
Moderate	1 (0.3)	5 (4.1)
Severe	0	5 (4.1)
Any TEAE Leading to Study Drug Discontinuation	2 (0.6) 5	5 (4.1) 15
Death[d]	0	0

E = number of events; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; PD = pharmacodynamic; PK = pharmacokinetic; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Notes: All on-treatment TEAE that occurred within 30 days after the last treatment received are included in this table.
Note: RACE is currently ongoing. The information for ongoing subjects is up to the date of interim data cutoff.

a. Clinical Pharmacology Studies include: PAR-C10-005, CL1-11-007, CL1-11-012, CL1-11-013, CL1-11-017, SH-PTH-0001, PBR 930811, PBR 930812, C09-002, Mosekilde IIT PK/PD Substudy, CL1-11-009, and CL1-11-010.
b. Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT.
c. Excluding 2 subjects who received the zinc chloride investigational formulation of Natpara
d. Within 30 days after the last treatment received.

Table 31. Overall Summary of Treatment-emergent Adverse Events – Safety Population – REPLACE

Category	Placebo N=40 n (%)	Events	Natpara N=84 n (%)	Events
Any TEAE				
No	0		6 (6.7)	
Yes	40 (100.0)	321	78 (92.9)	807
TEAE highest severity				
Mild	14 (35.0)		24 (28.6)	
Moderate	21 (52.5)		40 (47.6)	
Severe	5 (12.5)		14 (16.7)	
TEAE highest relationship				
Not related	26 (65.0)		34 (40.5)	
Related	14 (35.0)		44 (52.4)	
TEAE leading to study drug discontinuation	0	0	3 (3.6)	14
Any TESAE	4 (10.0)	5	9 (10.7)	11
TESAE highest severity				
Mild	1 (2.5)		1 (1.2)	
Moderate	2 (5.0)		3 (3.6)	
Severe	1 (2.5)		5 (6.0)	
TESAE highest relationship				
Not related	4 (10.0)		8 (9.5)	
Related	0		1 (1.2)	
TEAE leading to death	0	0	0	0

N = total number of subjects; n = number of subjects in category specified; SAE= serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment emergent serious adverse event

Notes: Percentages are based on the number of Safety subjects in each treatment arm. This table contains counts of subjects and events. If a subject experienced more than one adverse event in a category, the subject was counted only once in that category. Each event was counted.

a. Including one subject who missed only the last dose of study drug and was recorded as a completer in the disposition tables and listings.

6.1.4 Serious Adverse Events

In the Clinical Pharmacology Studies, 1 subject experienced a TESAE of arterial thrombus in the right femoral artery, which the investigator considered probably not related to study drug. In the clinical studies in hypoparathyroidism, 10 of 121 Natpara-treated subjects (8.3%) experienced a total of 17 on-treatment TESAEs. No event was reported in more than 1 subject (Table 32).

Five Natpara-treated subjects in the efficacy and safety studies experienced a post-treatment TESAE (i.e., during 1 day and 30 days after the last dose). Of the 5 events, 3 were hypocalcemia, 1 was hypercalcemia and 1 subject developed pancreatitis.

Table 32. Summary of On-treatment Treatment-emergent Serious Adverse Events in Decreasing Order of Frequency - Safety Population, Efficacy and Safety Studies in Hypoparathyroidism

Adverse Event Grouping[a] or MedDRA Preferred Term	Natpara (Any Dose) N=121 n (%)
Back pain	1 (0.8)
Cellulitis[a]	1 (0.8)
Cerebrovascular accident	1 (0.8)
Chest discomfort	1 (0.8)
Diarrhoea	1 (0.8)
Diverticulitis	1 (0.8)
Dyspnoea	1 (0.8)
Fracture[a,b]	1 (0.8)
Gastroenteritis	1 (0.8)
Hypercalcaemia[a]	1 (0.8)
Hypocalcaemia[a]	1 (0.8)
Lung adenocarcinoma metastatic	1 (0.8)
Syncope	1 (0.8)
Throat tightness	1 (0.8)
Viral infection	1 (0.8)
Vomiting	1 (0.8)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TESAE = treatment-emergent serious adverse event
Notes: Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. RACE is currently ongoing. The information for ongoing subjects is up to the date of interim data cutoff. All on-treatment TESAE that occurred within 30 days after the last treatment received are included in this table.
a. Adverse Event Groupings represent medically similar terms.
b. Radius and ulna fractures were reported for the same subject.

6.1.5 Adverse Events Associated With Discontinuation

In the efficacy and safety studies, 5 subjects discontinued treatment due to a TEAE with 3 of these occurring in REPLACE. With the exception of arthralgia (2 subjects, 1.7%), no other event was reported in 2 or more subjects (Table 33).

Table 33. Summary of On-treatment Treatment-emergent Adverse Events Leading to Drug Discontinuation of Natpara in Decreasing Order of Frequency - Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

Adverse Event Grouping[a] or MedDRA Preferred Term	Natpara (Any dose) N=121 n (%)
Arthralgia	2 (1.7)
Anxiety symptoms[a]	1 (0.8)
Asthenia	1 (0.8)
Cerebrovascular accident	1 (0.8)
Cognition and attention disorders and disturbances[a]	1 (0.8)
Decreased appetite	1 (0.8)
Depressive disorders[a]	1 (0.8)
Headaches[a]	1 (0.8)
Injection site reactions[a]	1 (0.8)
Lung adenocarcinoma metastatic	1 (0.8)
Nausea	1 (0.8)
Pain in extremity	1 (0.8)
Rash	1 (0.8)
Tetany[a]	1 (0.8)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TEAE = treatment-emergent adverse event.
Notes: Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. RACE is currently ongoing. All on-treatment TEAE that occurred within 30 days after the last treatment received that led to drug discontinuation are included in this table. The information for ongoing subjects is up to the date as of the interim data cutoff. One subject discontinued study drug, but had not formally discontinued from study prior to interim data cutoff.
a. Adverse Event Groupings represent medically similar terms.

6.1.6 Treatment-Emergent Adverse Events

In REPLACE, on-treatment TEAEs reported in ≥5% of the Natpara-treated subjects and at a rate ≥ 2-fold greater than placebo were hypercalcemia (19.0% vs. 2.5%), diarrhea (11.9% vs. 2.5%), vomiting (11.9% vs. 0%), anxiety symptoms 7.1% vs. 0%), hypomagnesemia (7.1% vs. 0%), and neck pain (6.0% vs. 2.5%) (Table 34). The only TEAE reported in ≥5% of the placebo-treated subjects and at a rate ≥ 2-fold greater than Natpara was fatigue (20.0% vs. 9.5%).

The most frequently reported (≥ 5% of subjects in either group) on-treatment TEAEs in the Efficacy and Safety studies in Hypoparathyroidism are summarized in Table 35.

The time of first occurrence of TEAEs was also examined (Table 36). The TEAEs with the highest incidence rates in the first week were nausea and headaches (reported by 9.1% and 6.6% of subjects, respectively). Except for hypocalcemia, influenza, lower respiratory tract infection, and urolithiasis, first onset incidence tended to decrease after

Week 12. The first onset of hypocalcemia had its highest rate in the ≥ 52- to <104-week time interval (14.9% of subjects).

Hypercalcemia, hypocalcemia, and hypercalciuria are discussed in detail, as adverse events of special interest (AESI), in Section 6.3.

Table 34. Summary of On-treatment Treatment-emergent Adverse Events Reported in ≥ 5% Natpara Subjects in Descending Order for Natpara – Safety Population – REPLACE

Adverse Event Grouping[a] or MedDRA Preferred Term	Placebo N=40 n (%)	Natpara (50/75/100 µg) N=84 n (%)
Paraesthesia[a]	16 (40.0)	33 (39.3)
Tetany[a]	16 (40.0)	28 (33.3)
Hypocalcaemia[a]	9 (22.5)	23 (27.4)
Headaches[a]	9 (22.5)	22 (26.2)
Upper respiratory tract infection[a]	12 (30.0)	17 (20.2)
Nausea	7 (17.5)	15 (17.9)
Hypercalcaemia[a]	1 (2.5)	16 (19.0)
Abdominal pain[a]	4 (10.0)	10 (11.9)
Diarrhoea	1 (2.5)	10 (11.9)
Vomiting	0	10 (11.9)
Arthralgia	4 (10.0)	9 (10.7)
Hypercalciuria[a]	3 (7.5)	9 (10.7)
Back pain	7 (17.5)	8 (9.5)
Cognition and attention disorders and disturbances[a]	3 (7.5)	8 (9.5)
Fatigue	8 (20.0)	8 (9.5)
Injection site reactions[a]	6 (15.0)	8 (9.5)
Pain in extremity	3 (7.5)	8 (9.5)
Anxiety symptoms[a]	0	6 (7.1)
Hypomagnesaemia[a]	0	6 (7.1)
Hypertension	2 (5.0)	5 (6.0)
Myalgia	3 (7.5)	5 (6.0)
Neck pain	1 (2.5)	5 (6.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TEAE = Treatment emergent adverse event
Notes: All on-treatment TEAE that occurred within 30 days after the last treatment received are included in this table.
a. Adverse Event Groupings represent medically similar terms.

Table 35. Summary of On-treatment Treatment-emergent Adverse Events Reported in ≥ 5% of Subjects - Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

Adverse Event Grouping[a] or MedDRA Preferred Term	Natpara (Any dose) N=121 n (%)
Paraesthesia[a]	52 (43.0)
Tetany[a]	42 (34.7)
Hypocalcaemia[a]	41 (33.9)
Headaches[a]	34 (28.1)
Upper respiratory tract infection[a]	31 (25.6)
Nausea	30 (24.8)
Hypercalcaemia[a]	28 (23.1)
Arthralgia	21 (17.4)
Abdominal pain[a]	19 (15.7)
Diarrhoea	18 (14.9)
Fatigue	17 (14.0)
Cognition and attention disorders and disturbances[a]	16 (13.2)
Vomiting	16 (13.2)
Back pain	15 (12.4)
Pain in extremity	15 (12.4)
Vitamin D decreased	14 (11.6)
Hypercalciuria[a]	13 (10.7)
Injection site reactions[a]	13 (10.7)
Anxiety symptoms[a]	12 (9.9)
Hypertension	11 (9.1)
Influenza[a]	11 (9.1)
Lower respiratory tract infection[a]	11 (9.1)
Myalgia	10 (8.3)
Constipation	9 (7.4)
Palpitations	9 (7.4)
Vitamin D deficiency	9 (7.4)
Chest discomfort	8 (6.6)
Hypomagnesaemia[a]	8 (6.6)
Neck pain	8 (6.6)
Urinary tract infections[a]	8 (6.6)
Dyspnoea	7 (5.8)
Sleep disorders and disturbances[a]	7 (5.8)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group

Notes: Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. RACE is ongoing with an interim. Information for ongoing subjects is up to the date of interim data cutoff. All on-treatment TEAE that occurred within 30 days after the last treatment received are included in this table.

a. Adverse Event Groupings represent medically similar terms.

Table 36. On-treatment Treatment-emergent Adverse Events by Time to First Onset (Reported in ≥ 5% of Natpara-Treated Subjects in Any Time Interval) - Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

	Time of Onset						
Adverse Event Grouping[a] or MedDRA Preferred Term	**< 1 week N=121 n (%)**	**≥ 1 to < 12 weeks N=121 n (%)**	**≥ 12 to < 24 weeks N=116 n (%)**	**≥ 24 to < 52 weeks N=108 n (%)**	**≥ 52 to < 104 weeks N=47 n (%)**	**≥ 104 to < 156 weeks N=44 n (%)**	**≥ 156 weeks N=5 n (%)**
Paraesthesia[a]	5 (4.1)	30 (24.8)	15 (12.9)	0	2 (4.3)	0	0
Tetany[a]	4 (3.3)	25 (20.7)	6 (5.2)	4 (3.7)	3 (6.4)	0	0
Hypocalcaemia[a]	1 (0.8)	11 (9.1)	13 (11.2)	9 (8.3)	7 (14.9)	0	0
Headaches[a]	8 (6.6)	20 (16.5)	2 (1.7)	1 (0.9)	2 (4.3)	1 (2.3)	0
Upper respiratory tract infection[a]	1 (0.8)	18 (14.9)	6 (5.2)	5 (4.6)	1 (2.1)	0	0
Nausea	11 (9.1)	9 (7.4)	3 (2.6)	1 (0.9)	4 (8.5)	2 (4.5)	0
Hypercalcaemia[a]	2 (1.7)	16 (13.2)	8 (6.9)	0	1 (2.1)	1 (2.3)	0
Arthralgia	1 (0.8)	11 (9.1)	5 (4.3)	3 (2.8)	1 (2.1)	0	0
Abdominal pain[a]	3 (2.5)	8 (6.6)	4 (3.4)	3 (2.8)	1 (2.1)	0	0
Diarrhoea	0	7 (5.8)	3 (2.6)	5 (4.6)	2 (4.3)	1 (2.3)	0
Fatigue	1 (0.8)	12 (9.9)	2 (1.7)	1 (0.9)	1 (2.1)	0	0
Cognition and attention disorders and disturbances[a]	2 (1.7)	9 (7.4)	0	4 (3.7)	1 (2.1)	0	0
Vomiting	1 (0.8)	7 (5.8)	2 (1.7)	4 (3.7)	2 (4.3)	0	0
Back pain	0	7 (5.8)	2 (1.7)	1 (0.9)	4 (8.5)	1 (2.3)	0
Pain in extremity	0	6 (5.0)	6 (5.2)	2 (1.9)	1 (2.1)	0	0
Influenza[a]	0	1 (0.8)	3 (2.6)	0	7 (14.9)	0	0
Lower respiratory tract infection[a]	0	1 (0.8)	2 (1.7)	5 (4.6)	3 (6.4)	0	0
Palpitations	0	7 (5.8)	0	2 (1.9)	0	0	0
Vitamin D deficiency	0	2 (1.7)	0	4 (3.7)	3 (6.4)	0	0
Urolithiasis[a]	0	0	1 (0.9)	0	3 (6.4)	1 (2.3)	0

Table 36. On-treatment Treatment-emergent Adverse Events by Time to First Onset (Reported in ≥ 5% of Natpara-Treated Subjects in Any Time Interval) - Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

	Time of Onset						
Adverse Event Grouping[a] or MedDRA Preferred Term	**< 1 week N=121 n (%)**	**≥ 1 to < 12 weeks N=121 n (%)**	**≥ 12 to < 24 weeks N=116 n (%)**	**≥ 24 to < 52 weeks N=108 n (%)**	**≥ 52 to < 104 weeks N=47 n (%)**	**≥ 104 to < 156 weeks N=44 n (%)**	**≥ 156 weeks N=5 n (%)**

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects with exposure at the start of the exposure interval; n = number of subjects with time to first onset with the specified event in the exposure interval; TEAE = treatment-emergent adverse event

Note: Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. Exposure intervals are based on actual time on drug and do not include breaks between studies. All on-treatment TEAE that occurred within 30 days after the last treatment received are included in this table. For each specified event, a subject may only be counted once, under the time interval in which the event first occurred. RACE is currently ongoing. The information for ongoing subjects is up to the date of interim data cutoff.

a. Adverse Event Groupings represent medically similar terms.

6.1.7 Adverse Drug Reactions

Unlike an adverse event, an adverse drug reaction (ADR) is an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all AEs observed during use of a drug and begins the judgment process. Only those terms, for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event, should be considered as an adverse reaction.

To identify these possible ADRs, 2 criteria were applied to the full set of on-treatment TEAEs. First, the most commonly occurring TEAEs among Natpara subjects in the efficacy and safety studies were identified by selecting those TEAEs that occurred in at least 5% of Natpara-treated subjects in the REPLACE study. Similar to the other summaries, the initial list of TEAEs screened for possible ADRs was limited to those AEs that occurred while subjects were receiving treatment, since the AEs that occurred after treatment was stopped were likely the result of drug discontinuation and re-titration of oral calcium and active vitamin D and not likely related to treatment. Second, to preliminarily determine whether an ADR was related to treatment with Natpara, the list was subsequently filtered to identify only those TEAEs occurring more frequently in Natpara-treated subjects compared with placebo. The resulting list and frequency of possible ADRs that meet these 2 criteria are displayed in Table 37.

Table 37. On-treatment Treatment-emergent Adverse Events (AE Grouping or MedDRA Preferred Term) Reported in ≥ 5% of rhPTH(1-84)-treated Hypoparathyroidism Subjects with Incidence in the rhPTH(1-84) Group Greater than the Placebo Group – Safety Population – REPLACE

Adverse Event Grouping[a] or MedDRA Preferred Term	Placebo (N=40) n (%)	Natpara (N=84) n (%)
Headaches[a]	9 (22.5)	22 (26.2)
Hypocalcemia[a]	9 (22.5)	23 (27.4)
Nausea	7 (17.5)	15 (17.9)
Hypercalcaemia[a]	1 (2.5)	16 (19.0)
Diarrhoea	1 (2.5)	10 (11.9)
Abdominal pain	4 (10.0)	10 (11.9)
Cognition and attention disorders and disturbances[a]	3 (7.5)	8 (9.5)
Hypercalciuria[a]	3 (7.5)	9 (10.7)
Vomiting	0	10 (11.9)
Arthralgia	4 (10.0)	9 (10.7)
Pain in extremity	3 (7.5)	8 (9.5)
Anxiety symptoms[a]	0	6 (7.1)
Hypomagnesaemia[a]	0	6 (7.1)
Hypertension	2 (5.0)	5 (6.0)
Neck pain	1 (2.5)	5 (6.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group

a. Adverse Event Groupings represent medically similar terms.

6.1.8 Post-treatment TEAEs

Overall, there were 121 subjects treated with Natpara that were followed for post-treatment TEAEs (i.e., after the last dose of study drug and ≤ 30 days after the last dose). Paresthesia (25 subjects, 20.7%), hypocalcemia (24 subjects, 19.8%), and tetany (14 subjects, 11.6%) were reported in ≥ 10% of the 121 subjects.

In REPLACE, subjects randomized to Natpara reported more TEAEs during post-treatment period than placebo-treated subjects. Paresthesia (21.4% Natpara, 5.0% placebo), hypocalcemia (26.2% Natpara, 7.5% placebo), and tetany (11.9% Natpara, 0 placebo) were the most common TEAEs.

6.1.9 Analysis of Laboratory Data

This section presents findings for laboratory analytes other than serum and urinary calcium which are presented in Section 6.3. Shift from normal at baseline to out of the normal reference range at endpoint are shown in Table 38 (for which a shift among Natpara-treated subjects in REPLACE was > 5% and 2-fold greater than in the placebo group).

WBC

In REPLACE, 13.8% of subjects in the Natpara group and none in the placebo group had normal white blood cell (WBC) counts at baseline that shifted to low (i.e., below the LLN) at endpoint. The mean change from baseline in WBC was -0.35 (± 2.041) x 10^9/L. This shift from a normal to low WBC count was not seen in RELAY, nor was there evidence of a dose-response trend between the 25-µg and 50-µg groups. This shift was also not observed in Studies RACE and REPEAT. In RACE, more subjects (5/6 [83.3%]) shifted from low to normal than from normal to low (9/84 [13.8%]).

To evaluate the clinical relevance of the finding, the AE data were examined. The rate of overall infections was somewhat higher in the placebo group (57.5%, 23/40) than in the Natpara group (32.1%, 27/84) in REPLACE. In patients with decrease in WBC, there were no TEAEs suggesting clinical events occurred because of the decrease.

Hematocrit

In REPLACE, 14.3% of subjects in the Natpara group and 3.6% in the placebo group had normal hematocrit counts at baseline that shifted to low at endpoint. The mean change from baseline in hematocrit was -0.002 (± 0.030) V/V. The shift to low hematocrit in REPLACE was not accompanied by a shift to low hemoglobin (1.5% of Natpara-treated subjects). Shift from normal at baseline to low at endpoint was also observed in RELAY (22% at 25 µg and 21% at 50 µg) and in RACE (4.9%), but not seen in REPEAT.

Hypocalcemia and hypercalcemia were defined as adverse events of special interest (AESI) for more detailed analysis of safety, based on AE reporting, as discussed in Section 6.4.

Magnesium

In REPLACE, 14.6% of subjects treated with Natpara vs. none in the placebo group had a magnesium concentration that was normal at baseline and low at endpoint (Table 38). The mean change from baseline in magnesium was -0.26 (± 0.215) mg/dL. This shift from normal at baseline to low at endpoint was also observed in REPEAT and RACE, but not seen in RELAY. Hypomagnesemia was reported as an adverse event more frequently in the Natpara group than in the placebo group in REPLACE (3.6% [3/84] vs. 0%, respectively).

Uric Acid

Shifts from normal to high for uric acid occurred in 12.2% of Natpara-treated subjects versus none of the placebo-treated subjects in REPLACE (Table 38). The mean change from baseline in uric acid was 0.70 (± 1.135) mg/dL. In RELAY, subjects treated with Natpara also had shifts in uric acid from normal at baseline to high at endpoint (6.7% in the 25 µg dose group and 15.0% in the 50 µg dose group). Similar shifts were observed in RACE and REPEAT (30.0% and 8.3%, respectively). There was only 1 (of 121, 0.8%) on-treatment adverse event of gout across the NSP development program in Hypoparathyroidism. In the much larger placebo-controlled studies in osteoporosis, 6 cases of gout (0.4%) were reported with placebo and 1 case (0.1%) with Natpara.

Alkaline Phosphatase

Overall, there was a shift from normal at baseline to high at endpoint in alkaline phosphatase concentrations in 25.0% of subjects treated with Natpara across all Efficacy and Safety Studies in Hypoparathyroidism (Table 38), likely reflecting the increase in BSAP due to activation of bone metabolism. The mean change from baseline in alkaline phosphatase was 58.5 (± 44.42) U/L. In REPLACE, this shift in alkaline phosphatase occurred in 25.3% of subjects in the Natpara group and 0% in the placebo group. In RELAY, this shift from normal at baseline to high at endpoint was seen in both dose groups with the highest occurrence in the highest dose group (11.1% in the 25-µg dose group and 20.0% in the 50-µg dose group). In addition, this shift was observed in 34.1% and 12.5% of subjects in RACE and REPEAT, respectively.

Creatinine Clearance

Creatinine clearance was estimated at baseline and endpoint using the Cockcroft-Gault formula. Subjects were categorized according to the 5 stages of the severity of chronic kidney disease classification based on the estimated creatinine clearance (Stage 1: ≥ 90 mL/min, Stage 2: 60-89 mL/min, Stage 3: 30-59 mL/min, Stage 4: 15-29 mL/min, Stage 5: < 15 mL/min). Renal function remained stable in REPLACE: 4 Natpara-treated subjects (5.1%) shifted from Stage 1 (normal) at Baseline to Stage 2 (mild decrease in estimated glomerular filtration rate [eGFR]) at Week 24 and 3 subjects (3.8%) shifted from mild at Baseline to moderate (Stage 3) at Week 24. The exactly same numbers of subjects had the opposite shifts. Renal function appeared stable with chronic treatment with Natpara, as observed in RACE (Table 41).

Table 38. Summary of Shifts from Normal at Baseline to Endpoint for White Blood Cells, Hematocrit, Magnesium, Uric Acid, and Alkaline Phosphatase

	REPLACE		RELAY		RACE	REPEAT	Total Efficacy and Safety Studies
Parameter Level at Endpoint[a]	**Placebo N=40**	**Natpara All Doses N = 84**	**Natpara 25 µg N=19**	**Natpara 50 µg N=23**	**Natpara All Doses N=49**	**Natpara All Doses N=24**	**Natpara All Doses N=121**
White blood cells	N = 28[b]	N = 65	N = 17	N = 21	N = 42	N = 20	N = 100
Low	0	9 (13.8)	2 (11.8)	2 (9.5)	2 (4.8)	1 (5.0)	4 (4.0)
Normal	26 (92.9)	55 (84.6)	15 (88.2)	19 (90.5)	39 (92.9)	19 (95.0)	95 (95.0)
High	2 (7.1)	1 (1.5)	0	0	1 (2.4)	0	1 (1.0)
Hematocrit	N = 28	N = 63	N = 18	N = 19	N = 41	N = 19	N = 97
Low	1 (3.6)	9 (14.3)	4 (22.2)	4 (21.1)	2 (4.9)	0	8 (8.2)
Normal	27 (96.4)	54 (85.7)	14 (77.8)	15 (78.9)	38 (92.7)	19 (100)	88 (90.7)
High	0	0	0	0	1 (2.4)	0	1 (1.0)
Magnesium	N=40	N=82	N=19	N=23	N=48	N=23	N=117
Low	0	12 (14.6)	1 (5.3)	0	5 (10.4)	4 (17.4)	15 (12.8)
Normal	40 (100)	70 (85.4)	18 (94.7)	23 (100)	43 (89.6)	19 (82.6)	102 (87.2)
High	0	0	0	0	0	0	0
Uric acid	N=33	N=74	N=15	N=20	N=40	N=24	N=104
Low	0	0	0	0	0	0	0
Normal	33 (100)	65 (87.8)	14 (93.3)	17 (85.0)	28 (70.0)	22 (91.7)	83 (79.8)
High	0	9 (12.2)	1 (6.7)	3 (15.0)	12 (30.0)	2 (8.3)	21 (20.0)
Alkaline phosphatase	N=36	N=79	N=18	N=20	N=44	N=24	N=112
Low	1 (2.8)	0	1 (5.6)	0	0	0	0
Normal	35 (97.2)	59 (74.7)	15 (83.3)	16 (80.0)	29 (65.9)	21 (87.5)	84 (75.0)
High	0	20 (25.3)	2 (11.1)	4 (20.0)	15 (34.1)	3 (12.5)	28 (25.0)

Table 38. Summary of Shifts from Normal at Baseline to Endpoint for White Blood Cells, Hematocrit, Magnesium, Uric Acid, and Alkaline Phosphatase

N = number of subjects in the treatment group; n = number of subjects in the specific baseline category and with non-missing endpoint category in the treatment group, and is used for the percentage. Subjects with missing category at baseline or endpoint are not summarized in the table.

a. Low, normal, or high relative to the reference range for the laboratory parameter.

b. Data for shift from normal are presented in this table. Data from subjects with high baseline values that shift to normal, or low baseline values that shift to normal are not shown. Therefore the N for each cell is less than the total number of subjects within a treatment group.

Note: Endpoint is defined as the last time point at which laboratory data were available. RACE is currently ongoing. The information for ongoing subjects is up to the date of interim data cutoff.

6.1.10 Analysis of Vital Signs and ECG Data

In REPLACE, in which vital signs were obtained at each visit, there were no clinically significant differences between Natpara and placebo in mean pulse, systolic blood pressure, and diastolic blood pressure over the 24-week study. The frequency of subjects with markedly abnormal vital sign values was low and comparable between treatment groups in REPLACE (Table 39). In RELAY, no markedly abnormal vital sign results were reported in either the 25-µg or the 50-µg treatment groups.

Table 39. Summary of Postbaseline Markedly Abnormal Vital Sign Results – Safety Population – REPLACE

Category	Natpara N=84		Placebo N=40	
	n	%	n	%
Systolic blood pressure (mm/HG)	N=84		N=40	
Decrease from baseline of ≥ 20 to ≤ 90	1	1%	1	3%
Decrease from baseline of ≥ 30 to ≤ 90	1	1%	0	0
Decrease from baseline of ≥ 40 to ≤ 90	1	1%	0	0
Increase from baseline of ≥ 20 to ≥ 180	1	1%	0	0
Increase from baseline of ≥ 30 to ≥ 180	1	1%	0	0
Increase from baseline of ≥ 40 to ≥ 180	0	0	0	0
Diastolic blood pressure (mm/HG)	N=84		N=40	
Decrease from baseline of ≥ 15 to ≤ 50	1	1%	1	3%
Decrease from baseline of ≥ 20 to ≤ 50	1	1%	0	0
Decrease from baseline of ≥ 25 to ≤ 50	0	0	0	0
Decrease from baseline of ≥ 30 to ≤ 50	0	0	0	0
Increase from baseline of ≥ 15 to ≥ 105	0	0	0	0
Increase from baseline of ≥ 20 to ≥ 105	0	0	0	0
Increase from baseline of ≥ 25 to ≥ 105	0	0	0	0
Increase from baseline of ≥ 30 to ≥ 105	0	0	0	0

N = total number of subjects; n = number of subjects in each abnormality category

In REPLACE, QTcF (QT interval corrected for heart rate by the Fridericia formula) decreased from -10.9 to -16.2 ms on average in the Natpara group at times when there were concurrent increases in serum calcium during the titration period. No effects on other cardiac intervals and durations (PR, QRS, RR) were observed.

In the Efficacy and Safety Studies in Hypoparathyroidism, no subjects treated with Natpara had abnormally low QTcF values < 370 ms. No subjects treated with Natpara had atrial fibrillation, ventricular fibrillation, or ventricular tachycardia.

There was also no evidence of a dose response in QTcF reduction observed in Study C09-002 that examined a 50 µg and 100 µg dose of Natpara. In C09-002, the postdose calcium concentrations were similar in the 2 dose groups even though exposure to PTH(1-84) was higher in the 100 µg treatment period.

Overall, the evidence suggests that the elevations in serum calcium in the hypoparathyroidism studies demonstrate the known effects of shortening of the QTc interval. It is unlikely that the on-treatment QTcF values, which were in the normal range, would incur an increased risk of arrhythmia; there is no evidence for such an acquired or drug-induced short QT syndrome.

6.1.11 Long-term Safety Experience with Natpara in RACE

The safety profile of Natpara in the open-label, long-term RACE was similar to that observed in the overall safety experience. In the 49 subjects enrolled in RACE, mean exposure to Natpara was 106.8 weeks (range, 5.9 to 129.7 weeks). After 2 years, 81.6% (40/49) of the subjects in RACE remained in the study.

Five subjects (10.2%) experienced at last 1 TESAE(s) with reported events consisting of viral infection, gastroenteritis, metastatic lung adenocarcinoma, syncope, fracture, dyspnea, and hypocalcemia, throat tightness, and chest discomfort (more than 1 AE could be reported per patient). The hypocalcemia event occurred in a 48-year old female about 1 year after she initiated Natpara treatment. She received IV calcium for serum calcium of 6.8 mg/dL and the event was reported to last 2 days. One subject (2.0%) discontinued study drug and then subsequently was discontinued from the study due to a TESAE of metastatic lung adenocarcinoma. There were no deaths in the study.

The most frequently reported TEAEs in RACE were: hypocalcemia, tetany, upper respiratory tract infection, paresthesia, nausea, and headache (Table 40).

Most subjects had stable renal function over 52 weeks of treatment with Natpara (Table 41). The estimated GFR of 1 subject placed them in a stage 2 chronic kidney disease (CKD) category at baseline and stage 3 at 1 year, and for 2 subjects stage 3 CKD at baseline and at 1 year.

Table 40. Summary of On-treatment Treatment-emergent Adverse Events Reported in ≥ 5% Natpara Subjects in Decreasing Frequency – Safety Population – RACE

Adverse Event Grouping[a] or MedDRA Preferred Term	Natpara N=49 n (%)
Tetany[a]	17 (34.7)
Hypocalcaemia[a]	17 (34.7)
Upper respiratory tract infection[a]	15 (30.6)
Paraesthesia[a]	14 (28.6)
Nausea	12 (24.5)
Headaches[a]	10 (20.4)
Abdominal pain[a]	9 (18.4)
Lower respiratory tract infection[a]	9 (18.4)
Arthralgia	7 (14.3)
Constipation	7 (14.3)
Diarrhoea	7 (14.3)
Influenza[a]	7 (14.3)
Pain in extremity	7 (14.3)
Vitamin D deficiency	7 (14.3)
Back pain	6 (12.2)
Cognition and attention disorders and disturbances[a]	6 (12.2)
Vomiting	6 (12.2)
Urinary tract infections[a]	6 (12.2)
Anxiety symptoms[a]	5 (10.2)
Chest discomfort	5 (10.2)
Fatigue	5 (10.2)
Hypercalcaemia[a]	5 (10.2)
Hypercalciuria[a]	5 (10.2)
Hypertension	5 (10.2)
Vitamin D decreased	5 (10.2)
Myalgia	4 (8.2)
Palpitations	4 (8.2)
Sleep disorders and disturbances[a]	4 (8.2)
Dyspnoea	3 (6.1)
Injection site reactions[a]	3 (6.1)
Neck pain	3 (6.1)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TEAE = Treatment emergent adverse event

Notes: All on-treatment TEAE that occurred within 30 days after the last treatment received are included in this table.

a. Adverse Event Groupings represent medically similar terms.

Table 41. Renal Function at Week 52 Compared to Baseline – Safety Population – RACE

	Baseline				
Stage at Week 52	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**
Stage 1	21 (54%)	1 (3%)	0	0	0
Stage 2	4 (10%)	10 (26%)	0	0	0
Stage 3	0	1 (3%)	2 (5%)	0	0
Stage 4	0	0	0	0	0
Stage 5	0	0	0	0	0

Stage of chronic kidney disease defined by NKF KDOQI guidelines, according to glomerular filtration rate (mL/min/1.73 m^2): stage 1, ≥ 90; stage 2, 60-89; stage 3, 30-59; stage 4, 15-29; stage 5, <15 (or dialysis) (http://www kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1 htm

Hypercalciuria (defined as 24-hour urinary calcium ≥ 300 mg/24 hr based on central laboratory evaluations define as > 300) is an important predictor for the development of renal stones. In RACE, 61% of patients at baseline had calcium excretion of > 300 mg/day. From Month 4 onwards Natpara treatment resulted in a gradual decrease in the percent of subjects with hypercalciuria, which is in line with the physiological action of PTH on calcium resabsorption (Table 42).

Table 42. Persistence of Effect – Reduction in Hypercalciuria – RACE

Visit for RACE Completers	Patients with Urine Ca > 300 mg/24 hours n/N	%
Baseline following REPLACE & RELAY	23/38	61%
Month 4	20/36	56%
Month 8	12/37	32%
Month 12	19/36	53%
Month 16	12/36	33%
Month 20	9/35	26%
Month 24	14/38	37%

Ca = calcium; N = total number of subjects completing Natpara treatment; n = number of subjects with hypercalciuria at timepoint shown

The persistence of hypercalciuria was assessed by looking at the number of incidences of urine calcium levels over 300 mg/24 hours for each subject who had measurements at Month 24 (n = 40). The incidence of hypercalciuria typically fluctuated over time, but most subjects did not have persistent hypercalciuria based on measurements at each of the 7 study visits (Table 43).

Table 43. Persistence of Hypercalciuria – RACE

Incidences of Hypercalciuria[a]	Number of Subjects	Percent of Subjects
≥ 4	9	22.5
≥ 5	7	17.5
≥ 6	4	10.0
≥ 7 (all visits)	4	10.0

a. Hypercalciuria is defined as a 24-hour urine calcium measurement of ≥ 300 mg/24 h
Note: The number of subjects with measurements of 24-hour urine at Month 24 = 40.

6.2 Osteoporosis Development Program

6.2.1 Extent of Exposure

The osteoporosis development program provides substantial supporting safety experience from 7 efficacy and safety studies of rhPTH(1-84) including experience from long-term extension studies (Table 58 in Appendix A lists the studies). Overall, 2864 subjects were treated with rhPTH(1-84) 100 µg/day for 3620.55 subject-years. Of the 2864 subjects, 2407 were treated for at least 1 year and 481 were treated for at least 2 years.

6.2.2 Demographic and Baseline Characteristics

All subjects enrolled in the osteoporosis clinical development program were female (Table 59 in Appendix A). Across studies of rhPTH(1-84), used alone or in combination, mean (SD) age was 64.6 (7.59) years; all of the subjects treated with rhPTH(1-84) were at least 45 years of age. The majority of subjects was white (84.5%) and was enrolled at a site in North America (65.9%).

6.2.3 Overall Safety Experience

Across the clinical studies in osteoporosis, 93.4% of 2864 subjects treated with rhPTH(1-84), either alone or in combination with other therapies, reported at least 1 TEAE, 7.0% experienced a TESAE, and 12.2% experienced a TEAE leading to discontinuation (Table 44). In the placebo-controlled studies, the proportion of placebo-treated subjects who experienced a TEAE (6.7%) was similar to the proportion of rhPTH(1-84)-treated subjects (8.1%).

Sixteen subjects died (2 placebo and 14 rhPTH[1-84]) across all experience. Of these, 7 rhPTH(1-84)-treated subjects died within 30 days of receiving their last treatment. An

additional 7 rhPTH(1-84)-treated subjects and 2 placebo subjects died more than 30 days after their last treatment.

Table 44. Overall Summary of On-treatment Treatment-emergent Adverse Events and Deaths - Safety Population – Efficacy and Safety Studies in Osteoporosis

Parameter	rhPTH(1-84) alone (Any dose) N=2715 n (%) E	rhPTH(1-84) in combination[a] (Any dose) N=149 n (%) E	rhPTH(1-84) alone or in combination[a] (Any dose) N=2864 n (%) E
Any TEAE	2539 (93.5) 23194	136 (91.3) 982	2675 (93.4) 24176
TEAE by Highest Severity			
Mild	594 (21.9)	25 (16.8)	619 (21.6)
Moderate	1473 (54.3)	92 (61.7)	1565 (54.6)
Severe	472 (17.4)	19 (12.8)	491 (17.1)
Any TESAE	197 (7.3) 316	4 (2.7) 7	201 (7.0) 323
TESAE by Highest Severity			
Mild	17 (0.6)	0	17 (0.6)
Moderate	54 (2.0)	1 (0.7)	55 (1.9)
Severe	126 (4.6)	3 (2.0)	129 (4.5)
Any TEAE Leading to Study Drug Discontinuation	328 (12.1) 504	21 (14.1) 38	349 (12.2) 542
Death[b]	7 (0.3) 10	0	7 (0.2) 10

E = number of events; N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Note: All on-treatment TEAE or TEAE with an outcome of death that occurred within 30 days after the last treatment received are included in this table. Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

a. In combination with alendronate or hormone replacement therapy.
b. Deaths include any TEAE with an outcome of death that occurred within 30 days after the last treatment received.

6.2.4 Mortality

Across the randomized controlled trials in osteoporosis, there were no deaths in placebo or in rhPTH(1-84)-treated subjects within 30 days of last treatment. There were 7 deaths reported in subjects treated with rhPTH(1-84) in long-term uncontrolled extension studies that were reported within 30 days of last treatment.

The TEAEs with an outcome of death included myocardial infarction, aortic dissection, disseminated intravascular coagulation, ovarian cancer, cachexia and liver metastases (both in the same subject), lung infection and pulmonary embolism (both in the same subject), and pneumonia and sepsis (both in the same subject). For the 1 subject who died due to lung infection and pulmonary embolism, the relationship of the event of pulmonary embolism to study drug was unknown.

An additional 7 rhPTH(1-84) subjects who experienced a TEAE died more than 30 days after receiving their last dose of study drug. The TEAEs were myocardial infarction (65 days post), death and dysarthria (93 days post), death and Creutzfeldt-Jakob Disease (CJD) (255 days post), subarachnoid hemorrhage (72 days post), renal cancer (31 days post), cardio-respiratory arrest (285 days post), and sudden death (35 days post).

NPS reviewed the case of CJD in detail and could not find substantive evidence for the diagnosis of CJD. Further, as noted in Section 3.1, control of potential adventitious agents in the manufacture of rhPTH(1-84) is exerted through control of raw materials, typical biological controls on the manufacturing process, and drug substance and drug product testing.

A listing of the deaths in the in Osteoporosis Development Program Brief is provided in Appendix B.

6.2.5 SAEs in Osteoporosis Development Program

Across all of the clinical studies in Osteoporosis, 7% of subjects treated with rhPTH(1-84) experienced an on-treatment TESAE. Across the placebo-controlled osteoporosis studies, a similar percentage of subjects in the rhPTH(1-84) group (5.3%) and in the placebo group (6.7%) experienced an on-treatment TESAE. The percentage of rhPTH(1-84)-treated subjects experiencing an on-treatment TESAE in the active-controlled osteoporosis studies and the uncontrolled osteoporosis studies, 5.6% and 5.8%, respectively, was similar to the percentage observed among rhPTH(1-84)-treated subjects in the placebo-controlled osteoporosis studies.

In the placebo-controlled osteoporosis studies, no TESAE occurred in more than 5 (0.3%) rhPTH(1-84)-treated subjects or 5 (0.4%) placebo subjects (Table 45). Across the total rhPTH(1-84) experience, the most common TESAE was hypercalcemia which was consistent the pharmacodynamic activity of rhPTH(1-84).

Table 45. Most Frequent (Reported in ≥ 3 Total rhPTH[1-84] Subjects) On-Treatment Treatment-Emergent Serious Adverse Events in Decreasing Frequency for All 2864 Subjects - Safety Population – Efficacy and Safety Studies in Osteoporosis

	Placebo Controlled Studies in Osteoporosis[a]		Active Controlled Studies in Osteoporosis[b]			Uncontrolled Studies in Osteoporosis[c]	Total Efficacy and Safety Studies in Osteoporosis[d]		
Adverse Event Preferred Term	Placebo N=1425 n (%)	rhPTH(1-84) alone (Any dose) N=1696 n (%)	rhPTH(1-84) alone (Any dose) N=119 n (%)	rhPTH(1-84) in combination[e] (Any dose) N=149 n (%)	rhPTH(1-84) alone or in combination[e] (Any dose) N=268 n (%)	rhPTH(1-84) alone (Any dose) N=1681 n (%)	rhPTH(1-84) alone (Any dose) N=2715 n (%)	rhPTH(1-84) in combination[e] (Any dose) N=149 n (%)	rhPTH(1-84) alone or in combination[e] (Any dose) N=2864 n (%)
Hypercalcaemia	0	5 (0.3)	1 (0.8)	0	1 (0.4)	4 (0.2)	10 (0.4)	0	10 (0.3)
Angina pectoris	4 (0.3)	2 (0.1)	1 (0.8)	0	1 (0.4)	4 (0.2)	7 (0.3)	0	7 (0.2)
Breast cancer	2 (0.1)	2 (0.1)	0	0	0	4 (0.2)	6 (0.2)	0	6 (0.2)
Non-cardiac chest pain	4 (0.3)	1 (0.1)	0	0	0	5 (0.3)	6 (0.2)	0	6 (0.2)
Atrial fibrillation	5 (0.4)	0	0	0	0	5 (0.3)	5 (0.2)	0	5 (0.2)
Chest pain	3 (0.2)	2 (0.1)	2 (1.7)	0	2 (0.7)	1 (0.1)	5 (0.2)	0	5 (0.2)
Pneumonia	2 (0.1)	2 (0.1)	0	0	0	3 (0.2)	5 (0.2)	0	5 (0.2)
Anaemia	0	4 (0.2)	0	0	0	0	4 (0.1)	0	4 (0.1)
Cholelithiasis	2 (0.1)	3 (0.2)	0	0	0	1 (0.1)	4 (0.1)	0	4 (0.1)
Colon cancer	1 (0.1)	3 (0.2)	0	0	0	1 (0.1)	4 (0.1)	0	4 (0.1)
Deep vein thrombosis	1 (0.1)	2 (0.1)	0	0	0	2 (0.1)	4 (0.1)	0	4 (0.1)
Foot fracture	3 (0.2)	2 (0.1)	0	0	0	2 (0.1)	4 (0.1)	0	4 (0.1)
Myocardial infarction	1 (0.1)	1 (0.1)	1 (0.8)	0	1 (0.4)	2 (0.1)	4 (0.1)	0	4 (0.1)
Small intestinal obstruction	1 (0.1)	1 (0.1)	0	0	0	3 (0.2)	4 (0.1)	0	4 (0.1)
Appendicitis	0	1 (0.1)	0	0	0	2 (0.1)	3 (0.1)	0	3 (0.1)
Back pain	1 (0.1)	2 (0.1)	0	1 (0.7)	1 (0.4)	0	2 (0.1)	1 (0.7)	3 (0.1)
Basal cell carcinoma	0	1 (0.1)	0	0	0	2 (0.1)	3 (0.1)	0	3 (0.1)

Table 45. Most Frequent (Reported in ≥ 3 Total rhPTH[1-84] Subjects) On-Treatment Treatment-Emergent Serious Adverse Events in Decreasing Frequency for All 2864 Subjects - Safety Population – Efficacy and Safety Studies in Osteoporosis

	Placebo Controlled Studies in Osteoporosis[a]		Active Controlled Studies in Osteoporosis[b]			Uncontrolled Studies in Osteoporosis[c]	Total Efficacy and Safety Studies in Osteoporosis[d]		
Adverse Event Preferred Term	Placebo N=1425 n (%)	rhPTH(1-84) alone (Any dose) N=1696 n (%)	rhPTH(1-84) alone (Any dose) N=119 n (%)	rhPTH(1-84) in combination[e] (Any dose) N=149 n (%)	rhPTH(1-84) alone or in combination[e] (Any dose) N=268 n (%)	rhPTH(1-84) alone (Any dose) N=1681 n (%)	rhPTH(1-84) alone (Any dose) N=2715 n (%)	rhPTH(1-84) in combination[e] (Any dose) N=149 n (%)	rhPTH(1-84) alone or in combination[e] (Any dose) N=2864 n (%)
Cellulitis	1 (0.1)	2 (0.1)	1 (0.8)	0	1 (0.4)	0	3 (0.1)	0	3 (0.1)
Cerebrovascular accident	0	1 (0.1)	1 (0.8)	0	1 (0.4)	1 (0.1)	3 (0.1)	0	3 (0.1)
Constipation	0	1 (0.1)	0	0	0	2 (0.1)	3 (0.1)	0	3 (0.1)
Coronary artery disease	3 (0.2)	2 (0.1)	0	0	0	1 (0.1)	3 (0.1)	0	3 (0.1)
Gastroenteritis	0	2 (0.1)	0	0	0	1 (0.1)	3 (0.1)	0	3 (0.1)
Gastrointestinal haemorrhage	1 (0.1)	2 (0.1)	0	0	0	1 (0.1)	3 (0.1)	0	3 (0.1)
Osteoarthritis	3 (0.2)	0	0	0	0	3 (0.2)	3 (0.1)	0	3 (0.1)
Supraventricular tachycardia	1 (0.1)	2 (0.1)	0	0	0	1 (0.1)	3 (0.1)	0	3 (0.1)
Syncope	0	0	0	0	0	3 (0.2)	3 (0.1)	0	3 (0.1)
Vomiting	1 (0.1)	2 (0.1)	0	0	0	1 (0.1)	3 (0.1)	0	3 (0.1)

N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TESAE = treatment emergent serious adverse event.

Note: All on-treatment TESAE and TESAE with an outcome of death which occurred within 30 days after the last treatment received are included in this table.

a. Placebo Controlled Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, and CL1-11-008.

b. Active Controlled Studies in Osteoporosis include: N01-AR-9-2245 and CL1-11-003.

c. Uncontrolled Studies in Osteoporosis include: CL1-11-002 and CL1-11-016.

d. Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

e. In combination with alendronate or hormone replacement therapy.

6.2.6 Adverse Events Associated With Discontinuation in Osteoporosis Development Program

The only on-treatment TEAEs leading to discontinuation in at least 1% of rhPTH(1-84)-treated subjects in the Osteoporosis Development Program were nausea (3.0%), headache (1.4%), and hypercalciuria (1.4%) (Table 60 in Appendix A). Within the placebo-controlled studies in osteoporosis, each of these on-treatment TEAEs led to discontinuation in a greater percentage of rhPTH(1-84)-treated subjects than placebo-treated subjects.

The majority of on-treatment TEAEs leading to discontinuation (nausea [60/86] and headache [29/40]) had their onset during the first 12 weeks of treatment. The majority (25/39) of cases of hypercalciuria leading to discontinuation had their onset after at least 24 weeks of treatment.

6.2.7 Treatment-Emergent Adverse Events

On-treatment TEAEs reported in ≥ 5% of rhPTH(1-84)-treated subjects are summarized in Table 61 (Appendix A). In the placebo-controlled osteoporosis studies, which included 1696 rhPTH(1-84)-treated subjects and 1425 placebo-treated subjects, the only on-treatment TEAEs for which the incidence rate in rhPTH(1-84)-treated subjects exceeded the incidence rate in placebo-treated subjects by 2-fold were hypercalcemia (22.9% rhPTH[1-84], 3.9% placebo) and nausea (20.2% rhPTH[1-84], 8.6% placebo).

6.2.8 Analysis of ECG Data

An ECG substudy of rhPTH(1-84) was conducted in StudyALX1-11-93001, an 18-month double-blind, placebo-controlled study. The primary objective of this retrospective assessment of centrally read ECGs was to evaluate whether hypercalcemia was associated with changes in ECG readings (especially initiation or exacerbation of cardiac arrhythmias and change in QT interval). Secondary objectives were to evaluate whether rhPTH(1-84) 100 µg/day treatment was associated with changes in any ECG parameters, including ECG diagnostic findings, and whether there was an interaction between the effects of rhPTH(1-84) and hypercalcemia on ECG parameters. A total of 200 subjects with hypercalcemia and 177 subjects without hypercalcemia were included in the substudy.

The findings of the substudy were as follows:

- At baseline, there were only small, not clinically meaningful, differences in ECG intervals among the 4 subgroups (rhPTH[1-84] subjects with hypercalcemia, rhPTH(1-84) subjects without hypercalcemia, placebo subjects with hypercalcemia, and placebo subjects without hypercalcemia), between the treatment groups (rhPTH[1-84] and placebo), and between the hypercalcemia groups.
- At baseline and on treatment, there were only minor differences in diagnostic coding among the subgroups. These differences were not clinically meaningful.

- In the analysis of hear rate (HR), PR interval changes, QRS axis, and QRS duration, small changes were observed, but none were considered clinically meaningful.
- QTc, by all 3 correction methods, decreased with treatment in the rhPTH(1-84) subjects with hypercalcemia and in the hypercalcemia group. The decreases were not clinically meaningful.
- No subject had a QTc > 501 msec and only 1 subject (an rhPTH[1-84] subject with hypercalcemia) experienced a QTc change (increase) of > 60 msec.

The conclusion of the study was that in the osteoporosis subjects studied, hypercalcemia appears to be associated with small, non-clinically meaningful, decreases in QTc interval, but minimal or no change in HR, PR interval, QRS axis, and QRS duration. rhPTH(1-84) does not appear to pose a cardiac electrophysiologic risk; i.e., cardiac rhythm and repolarization were not adversely affected, nor did rhPTH(1-84) affect intraventricular conduction.

Overall, the frequency of subjects with any treatment-emergent SAE was slightly lower in the rhPTH(1-84) group. Atrial fibrillation was reported as a TESAE in 5 placebo subjects and in no rhPTH(1-84) subjects. The incidence of other arrhythmia-related terms such as supraventricular tachycardia, ventricular extrasystoles, tachycardia and bradycardia were comparable between treatment groups. Additionally, the incidences of TESAEs of angina pectoris, myocardial infarction, coronary artery disease and angina unstable were comparable between treatment groups. Two subjects in the placebo group had TESAEs of hypertension while no subjects in the rhPTH(1-84) group had such reported.

6.2.9 Analysis of Laboratory Data

In the placebo-controlled osteoporosis studies:

- a greater percentage of subjects in the rhPTH(1-84) treatment group compared with the placebo group had a shift from normal at baseline to low at endpoint in hemoglobin (4.9% vs. 2.2%) and red blood cell (12.7% vs. 7.0%).
- a greater percentage of subjects in the rhPTH(1-84) group than in the placebo group had a shift from normal at baseline to high at endpoint in calcium (14.9% vs. 7.7%), alkaline phosphatase (28.0% vs. 4.7%), and uric acid (19.5% vs. 5.1%).
- the proportion of subjects who had shifts from normal at baseline to high at endpoint for 24-hour urine calcium was 2-fold higher in the rhPTH(1-84) group than the placebo group (15.4% vs. 7.4%).

6.3 Postmarketing Safety Experience

Postmarketing exposure data to rhPTH(1-84) (Preotact®) is estimated as 61,091 patient years through 24 April 2013. This amount of safety data to support a rare disease indication is uncommon and helps further inform the safety profile of Natpara for the treatment of hypoparathyroidism.

Review of the events reporting in the postmarketing experience did not reveal any safety concerns that would be unexpected in the patient population. There have been no regulatory actions taken by Nycomed or by the regulatory authorities for safety reasons.

There were 12 deaths identified through spontaneous postmarketing reports for Preotact in the treatment of osteoporosis. The reported AEs with an outcome of death were: 'acute myocardial infarction', 'death' (details unknown) – 6 subjects, 'cerebrovascular accident', 'pneumonia and heart failure', 'unresolving lower respiratory tract infection', 'cardiac arrest', 'renal and hepatic failure'.

A summary of the most frequent (reported in ≥ 10 subjects) spontaneously reported postmarketing serious adverse drug reactions (ADRs) from 24 April 2006 to 24 April 2013 in subjects receiving rhPTH(1-84) is provided in Table 46. There were no reports of osteosarcoma.

Table 46. Most Frequent (Reported in ≥ 3 Subjects) Spontaneously Reported Postmarketing Serious Adverse Drug Reactions from 24 April 2006 to 24 April 2013 - rhPTH(1-84)

Adverse Event Preferred Term	Number of Subjects
Hypercalcaemia	43
Nausea	40
Dizziness	28
Headache	24
Vomiting	22
Fatigue	19
Weight decreased	19
Blood alkaline phosphatase increased	16
Blood calcium increased	14
Hyperhidrosis	13
Palpitations	13
Spinal fracture	12
Dyspnoea	11
Decreased appetite	10
Tachycardia	10

ADR = adverse drug reaction; ICH = International Conference on Harmonisation

Note: In accordance with ICH E2C, all postmarketing spontaneous reports of adverse experiences, unless indicated otherwise by the reporting healthcare professional, should be assumed to be ADR.

6.4 Adverse Events of Special Interest

Because of the mechanism of action of Natpara, hypocalcemia, hypercalcemia, and hypercalciuria were defined as adverse events of special interest (AESI) for more detailed analysis of safety. AE grouping terms, combining MedDRA preferred terms that included increased/decreased laboratory values.

For hypocalcemia, the PTs used were hypocalcemia and blood calcium decreased (collectively referred to as AESI of hypocalcemia). For hypercalcemia, the PTs used were hypercalcemia and blood calcium increased collectively referred to as AESI of hypercalcemia). For hypercalciuria, the PTs used were hypercalciuria and urine calcium increased (collectively referred to as AESI of hypercalciuria).

This section also reviews the safety experience with the pen device used for injection, immunogenicity, and evaluates the potential for osteosarcoma based upon the rat carcinogenicity finding.

6.4.1 Hypocalcemia

6.4.1.1 REPLACE

6.4.1.1.1 Hypocalcemia Based on Adverse Events Reported in REPLACE

During the optimization period prior to randomization and treatment with study drug, 7 subjects (8.3%) who were eventually randomized to Natpara and 3 subjects (7.5%) who were eventually randomized to placebo experienced an AESI of hypocalcemia (Table 47).

During the treatment period, 27.4% of subjects in the Natpara group experienced an AESI of hypocalcemia compared to 22.5% of subjects in the placebo group. The investigator classified the severity of most on-treatment hypocalcemia events (42/43 in the Natpara and 9/9 in the placebo group) as mild or moderate.

No AESI of hypocalcemia reported during the on-treatment period met the regulatory definition of serious or led to discontinuation (Table 48).

To investigate the effect of sustained withdrawal of Natpara, on the last day of treatment baseline doses of oral calcium and active vitamin D were re-introduced while Natpara was withheld for the subsequent 4 week withdrawal period. After complete and sustained withdrawal of study drug at study end, 22 (28.0%) Natpara-treated subjects and 3 (9.0%) placebo-treated subjects experienced a new post-treatment AESI of hypocalcemia. In 2 Natpara-treated subjects and 1 placebo subject, the post-treatment hypocalcemia was considered serious, and each of these subjects required intravenous (IV) calcium gluconate. In addition, 3 Natpara-treated subjects with non-serious post-treatment AESIs of hypocalcemia required IV calcium infusion. These events occurred 2 to 8 days following treatment withdrawal. These findings demonstrate that sustained withdrawal of Natpara treatment in hypoparathyroidism subjects needs to be accompanied by

reinstitution of pharmacological doses of oral calcium and vitamin D and frequent monitoring of serum calcium.

Accidental missed doses were not associated with severe cases of hypocalcemia and therefore pose minimal risk to patients. During the on-treatment period with Natpara, 23 subjects missed at least 1 dose of Natpara on 36 occasions, according to their e-diaries. These missed doses of Natpara were associated with mild to moderate symptoms of hypocalcaemia in 4 patients. No ER visits were necessary and all events resolved. The risk of hypocalcemia when treatment with Natpara is interrupted is identified and described in the Risk Management Plan (Section 7.2) to alert prescribing physicians of this risk.

Table 47. Summary of AESI of Hypocalcemia by Study Period – Safety Population – REPLACE

	Placebo		Natpara	
Study Period	Subjects N=40 n (%)	Events	Subjects N=84 n (%)	Events
Optimization (before the first dose date)	3 (7.5)	4	7 (8.3)	15
Treatment (the first dose date to the last dose date)	9 (22.5)	9	23 (27.4)	43
Post-treatment	3 (9.4))	4	22 (27.8)	31

AESI = adverse event of special interest; N = total number of subjects in the treatment group; n = number of subjects with the event of interest during the active titration period
Notes: Hypocalcemia includes the AEs with the preferred terms of "hypocalcemia" and "blood calcium decreased". The optimization period includes pre-treatment (nontreatment-emergent) AEs only. The post-treatment period was after the last dose of study drug and ≤ 30 days after the last dose.

Table 48. Summary of Hypocalcemia as an Adverse Event of Special Interest – Safety Population – REPLACE

	On-treatment		Post-treatment	
Parameter	Placebo N=40 n (%)	Natpara N=84 n (%)	Placebo N=40 n (%)	Natpara N=84 n (%)
TEAE	9 (22.5)	23 (27.4)	3 (9.4)	22 (27.8)
TESAE	0	0	1 (2.5)	2 (2.4)
TEAE Leading to Discontinuation	0	0	0	0

N = number of subjects in the treatment group; n= number of subjects with the specified event in the treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Note: Hypocalcemia AEs include the AEs with the preferred terms of "Hypocalcaemia" and "Blood calcium decreased".
Note: The number of events reported do not include events ongoing from previous study periods, i.e., new events only

6.4.1.2 Adverse Events of Hypocalcemia in Hypoparathyroidism Development Program

6.4.1.2.1 Efficacy and Safety Studies in Hypoparathyroidism

Across all of the NPS clinical studies in hypoparathyroidism overall, including REPLACE, 41 (33.9%) of Natpara-treated subjects experienced an on-treatment AESI of hypocalcemia (Table 49). The maximum severity was mild or moderate for the majority of subjects who had an on-treatment AESI of hypocalcemia. Only 2 subjects (1 in REPLACE and 1 in REPEAT) had a severe on treatment AESI of hypocalcemia.

Table 49. Summary of Hypocalcemia as an Adverse Event of Special Interest – Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

	On-treatment
Parameters	**Natpara (Any dose) N=121 n (%)**
TEAE	41 (33.9)
TESAE	1 (0.8)
TEAE Leading to Discontinuation	0

N = number of subjects in the treatment group; n= Number of subjects with the specified event in the treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Notes: Hypocalcemia AESI includes preferred terms of "Hypocalcaemia" and "Blood calcium decreased". RACE is currently ongoing. The information for ongoing subjects is up to the date of interim data cutoff. Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. Post-treatment defined as after the last dose of study drug and ≤ 30 days after the last dose.

No subject had an on-treatment AESI of hypocalcemia that led to discontinuation and 1 subject had an on treatment TESAE of hypocalcemia that was treated with IV infusion in the hospital with no change in the dose of study drug (Table 49).

A total of 18.9% (25/132) of Natpara-treated subjects experienced a post-treatment AESI of hypocalcemia.

6.4.1.3 Adverse Events of Hypocalcemia in Osteoporosis Development Program

Across all of the Efficacy and Safety Studies in Osteoporosis, 1 subject had an on-treatment AESI of hypocalcemia. There were no on-treatment or post-treatment TESAEs of hypocalcemia or TEAEs of hypocalcemia that led to discontinuation. This low rate of hypocalcemia is consistent with expectations as the subjects with osteoporosis were all likely to have normal parathyroid function.

6.4.2 Hypercalcemia

6.4.2.1 REPLACE

6.4.2.1.1 Hypercalcemia Based on Adverse Events Reported in REPLACE

During the optimization period (pre-randomization), 3 subjects (3.6%) who were eventually randomized to Natpara and no subjects who were eventually randomized to placebo experienced an AESI of hypercalcemia (Table 50). These subjects all had on-treatment TEAEs of hypercalcemia and/or hypocalcemia.

Table 50. Summary of AESI of Hypercalcemia by Study Period – Safety Population – REPLACE

	Placebo		Natpara	
Study Period	Subjects N=40 n (%)	Events	Subjects N=84 n (%)	Events
Optimization (before the first dose date)	0	0	3 (3.6)	3
Treatment (the first dose date to the last dose date)	1 (2.5)	1	16 (19.0)	19
Post-treatment	3 (7.5)	3	2 (2.4)	2

AESI = adverse event of special interest; CRF = case report form; N = total number of subjects in the treatment group; n= number of subjects with the event of interest during the active titration period

Notes: Hypercalcemia includes the AEs with the preferred terms of "hypercalcemia" and "blood calcium increased". The optimization period includes pre-treatment (nontreatment-emergent) AEs only. The post-treatment period was after the last dose of study drug and ≤ 30 days after the last dose.

Sixteen subjects (19.0%) in the Natpara group and 1 subject (2.5%) in the placebo group had an on-treatment AESI of hypercalcemia. Events occurred primarily during the initial titration period when most adjustments in study drug and oral calcium/active vitamin D occurred.

During the titration period (through Week 12), 12 Natpara-treated subjects (14.3%) and 1 placebo subject (2.5%) experienced an AESI of hypercalcemia. Two of the events occurred 2 and 3 days after the initiation of Natpara 50 µg, however all others occurred well into the titration period ranging between Study Day 25 and Study Day 57, following up-titration to 75 or 100 µg of Natpara.

Of the 12 Natpara-treated subjects who experienced an AESI of hypercalcemia during the titration period, 10 of the subjects had events that were mild, 1 that was moderate, and 1 that was severe and reported as a TESAE with an interruption of study drug. All of these events resolved, with the majority (8 events) having a duration of ≤ 7 days and only 1 of these subjects had study drug dose decreased in response to the hypercalcemia. Of the 4 subjects who had events with durations > 7 days (range: 15 to 58 days), 2 subjects interrupted study drug regimen for 2 to 3 times for 1 or 2 days at a time.

Three subjects had 2 episodes of hypercalcemia; 1 had a mild episode of hypercalcemia that started at the end of the titration period and lasted for 28 days, 1 had a mild episode during the same time period, which resolved after 20 days, and 1 had a severe episode in the stable period that lasted 5 days and necessitated an interruption in study drug. The subject completed the study and subsequently enrolled in RELAY and RACE.

During the treatment period, 16 (19.5%) Natpara-treated subjects had 19 AESIs of hypercalcemia compared to 1 (2.5%) placebo subject (Table 50). Hypercalcemic events were primarily mild or moderate and resolved quickly. One subject had a severe event that resulted in an interruption of the Natpara dose (100 µg).

After complete and sustained withdrawal of study drug, 3 placebo subjects and 2 Natpara-treated subjects experienced a post-treatment AESI of hypercalcemia. Among the Natpara-treated subjects, 1 had a post-treatment TESAE of hypercalcemia and 1 had a post-treatment AESI of hypercalcemia that led to discontinuation (i.e., the event of hypercalcemia was recorded 1 day after the date of the last dose of Natpara). In addition, 1 subject in the placebo group who did not have an AESI of hypercalcemia *per se*, had an ACSC concentration at Visit 16 of 12.7 mg/dL that was secondary to the post-treatment TESAE of dehydration and unrelated to study drug.

6.4.2.2 Adverse Events of Hypercalcemia in Hypoparathyroidism Development Program

6.4.2.2.1 Efficacy and Safety Studies in Hypoparathyroidism

Across all of the NPS clinical studies in Hypoparathyroidism, 25.6% of Natpara-treated subjects experienced an on-treatment AESI of hypercalcemia (PTs of hypercalcemia and blood calcium increased) (Table 51). The maximum severity was mild or moderate for the majority of subjects who had an on-treatment AESI of hypercalcemia. Five subjects had severe events (2 in REPLACE) of an on-treatment AESI of hypercalcemia. No TEAEs of nephrocalcinosis or nephrolithiasis were reported during the on-treatment phase. No subjects in any of the Efficacy and Safety Studies in Hypoparathyroidism experienced an on-treatment AESI of hypercalcemia that led to discontinuation.

There were no placebo-treated subjects and only 1 Natpara-treated subject (from REPLACE) with an on-treatment TESAE of hypercalcemia.

Table 51. Summary of Hypercalcemia as an Adverse Event of Special Interest– Safety Population – Efficacy and Safety Studies in Hypoparathyroidism

	On-treatment	Post-treatment
Parameters	Natpara N=121 n (%)	Natpara N=121 n (%)
TEAE	29 (25.6)	2 (1.7)
TESAE	1 (0.8)	1 (0.8)
TEAE Leading to Discontinuation	0	1 (0.8)
Albumin-corrected Total Serum Calcium > 11.9 mg/dL	7 (5.8)	0

N = number of subjects in the treatment group; n= number of subjects with the specified event in the treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Notes: Hypercalcemia AEs includes the AEs with the preferred terms of "Hypercalcemia" and "Blood calcium increased". RACE is currently ongoing. The information for ongoing subjects is up to the date of interim data cutoff. Efficacy and Safety Studies in Hypoparathyroidism include: REPLACE, RELAY, RACE, and REPEAT. Post-treatment defined as after the last dose of study drug and ≤ 30 days after the last dose.

REPLACE allowed for a closer analysis of whether hypercalcemic events occurred during the titration period, where significant adjustments to oral calcium and active vitamin D doses were taking place, or during the stable phase with lesser changes. As expected, more AESIs of hypercalcemia occurred in the titration phase than in the stable phase, as a treatment balance between study drug titration and oral calcium and active vitamin D dose decreases was targeted. In the majority of cases, the events were transient, and in all but 1 case (the SAE of hypercalcemia, managed with saline infusion) managed by titration of study drug or adjustment of oral calcium and active vitamin D.

Two Natpara-treated subjects experienced a post-treatment AESI of hypercalcemia and 1 subject had a post-treatment AESI of hypercalcemia that led to discontinuation (i.e., the event of hypercalcemia was recorded 1 day after the date of the last dose of Natpara) (all in REPLACE).

6.4.2.3 Adverse Events of Hypercalcemia in Osteoporosis Development Program

Hypercalcemia Based on Adverse Events Reported

Across all of the Efficacy and Safety Studies in Osteoporosis, 27.7% of rhPTH(1-84)-treated subjects experienced an on-treatment AESI of hypercalcemia (Table 52). Less than 1% of rhPTH(1-84)-treated subjects had an on-treatment TESAE of hypercalcemia, and less than 1% had an on-treatment AESI of hypercalcemia that led to discontinuation. In addition, there were 6 rhPTH(1-84)-treated subjects who had a post-treatment event of hypercalcemia that led to discontinuation (the event [preferred

term (PT) of hypercalcemia] was recorded 1 day after the date of the last dose of rhPTH[1-84]).

Table 52. Summary of On-treatment Adverse Events of Special Interest – Hypercalcemia - Safety Population – Efficacy and Safety Studies in Osteoporosis

Parameter	rhPTH(1-84) N=2864 n (%)
TEAE	793 (27.7)
TESAE	11 (0.4)
TEAE Leading to Discontinuation	27 (0.9)
Albumin-corrected total serum calcium >11.9 mg/dL	59 (2.1)

N = number of subjects in the treatment group; n = number of subjects with the specified event in the treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
Notes: Hypercalcemia AEs includes the AEs with the preferred terms of "Hypercalcemia" and "Blood calcium increased". Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

6.4.3 Hypercalciuria

6.4.3.1 REPLACE

6.4.3.1.1 Hypercalciuria Based on Adverse Events Reported in REPLACE

During the optimization period (pre-randomization), 6 subjects (7.1%) who were eventually randomized to Natpara and 2 subjects (5.0%) who were eventually randomized to placebo experienced at least 1 AESI of hypercalciuria (Table 53). Eight Natpara subjects (9.5%) and 3 placebo subjects (7.5%) experienced at least 1 AESI of hypercalciuria during Weeks 1 through 12 (titration period), as did 8 (Natpara-treated subjects (9.5%) and 2 placebo subjects (5.0%) during the stable period. Five (6.0%) and 2 (5.0%) in the Natpara and placebo groups, respectively, experienced an AESI of hypercalciuria during the post-treatment period.

Table 53. Summary of AESI of Hypercalciuria by Study Period – Safety Population – REPLACE

	Placebo		Natpara	
Study Period **Adverse Event of Interest**	**Subjects N=40** **n (%)**	**Events**	**Subjects N=84** **n (%)**	**Events**
Optimization (before the first dose date)	2 (5.0)	2	6 (7.1)	6
Treatment (the first dose date to the last dose date)	3 (7.5)	4	9 (10.7)	10
Post-treatment	2 (5.0)	2	5 (6.0)	5

AE = adverse event; N = total number of subjects in the treatment group; n= number of subjects with the event of interest during the active titration period

Notes: Hypercalciuria includes the AEs with the preferred terms of "hypercalciuria" and "urine calcium increased". The optimization period includes pre-treatment (nontreatment-emergent) AEs only. Post-treatment defined as after the last dose of study drug and ≤ 30 days after the last dose.

6.4.3.1.2 Hypercalciuria Based on 24-Hour Urine Calcium Excretion in REPLACE

During the optimization period of REPLACE, a stringent regimen of oral calcium and vitamin D was introduced so that subjects reached their target serum calcium concentration goal of 8 to 9 mg/dL, such that they could be randomized. As a consequence, more than half of subjects experienced hypercalciuria (defined as 24-hour urinary calcium ≥ 300 mg/24 hr based on central laboratory evaluations) prior to randomization. Mean 24-hour calcium excretion was 283 mg/24 h at screening and 354 mg/24 h at randomization, confirming the inability to reach target serum calcium concentration with oral calcium and vitamin D alone without also increasing urinary calcium excretion.

Hypercalciuria in subjects who completed REPLACE decreased from 57% at baseline to 34% at study end among subjects treated with Natpara and less so (from 49% to 39%) in placebo subjects (Table 54). Among those with hypercalciuria at baseline, 32% in the Natpara group vs. 24% in the placebo group showed improvement over the study, with urinary calcium excretion ≤ 300 mg/24 hr at Week 24. And, among those with normal urinary calcium excretion at baseline, fewer Natpara-treated subjects shifted to high daily excretion (10% vs. 15% placebo subjects).

Table 54. Summary of Hypercalciuria (24-hour Urine Calcium ≥ 300 mg/24hr) for Subjects Who Completed REPLACE

Changes in 24-hour Urine Ca (mg/day) from Baseline to Week 24	Natpara N=74		Placebo N=33	
	n	%	n	%
Patients with > 300mg/day at baseline	42	57%	16	48%
Patients with > 300mg/day at Week 24	25	34%	13	39%
From > 300 to ≤ 300 (high to normal)	24	32%	8	24%
From ≤ 300 to > 300 (normal to high)	7	9%	5	15%

N= total number of subjects; n = number of subjects with available 24-hour urine calcium data at both baseline the corresponding visit week

6.4.3.2 Adverse Events of Hypercalciuria in Hypoparathyroidism Development Program

6.4.3.2.1 Efficacy and Safety Studies in Hypoparathyroidism

Across the clinical studies in Hypoparathyroidism, 15 Natpara-treated subjects (11.4%) experienced an on-treatment AESI of hypercalciuria. The maximum severity was mild for the majority of subjects who had an on-treatment TEAE of hypercalciuria. No subjects had a severe on-treatment TEAE of hypercalciuria. No subjects experienced an on-treatment AESI of hypercalciuria that was serious or led to discontinuation. Four subjects, all in REPLACE, experienced hypercalcemia concurrently with the hypercalciuria.

No subjects in any of the Efficacy and Safety Studies in Hypoparathyroidism experienced any post-treatment AESIs of hypercalciuria.

6.4.3.3 Adverse Events of Hypercalciuria in Osteoporosis Development Program

Across the clinical studies in Osteoporosis, 43.4% of rhPTH(1-84)-treated subjects experienced an on-treatment AESI of hypercalciuria (Table 55). One subject had an on-treatment TESAE of hypercalciuria and 1 additional subject experienced a post-treatment TESAE of hypercalciuria. Few (1.4%) rhPTH(1-84)-treated subjects experienced an on-treatment AESI of hypercalciuria that led to discontinuation. Fourteen

subjects (0.4%) experienced a post-treatment AESI of hypercalciuria that led to discontinuation (the event [PT of hypercalciuria] was recorded 1 day after the date of the last dose of rhPTH[1-84]).

Table 55. Summary of On-treatment Adverse Events of Special Interest - Hypercalciuria - Safety Population, Total Efficacy and Safety Studies in Osteoporosis

Parameter	rhPTH(1-84) N=2864 n (%)
TEAE	1242 (43.4)
TESAE	1 (0.0)
TEAE Leading to Discontinuation	39 (1.4)

N = number of subjects in the treatment group; n = number of subjects with the specified event in the treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
Notes: Hypercalciuria includes the AEs with the preferred terms of "Hypercalciuria" and "Urine calcium increased". Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

6.4.4 Pen Complaints and Adverse Events

In the NPS clinical studies in Hypoparathyroidism, the Natpara® Q-Cliq™ and the Ypsomed pen were both used in RACE, whereas only the Ypsomed pen was used in Studies REPLACE, RELAY, and REPEAT. Both pens were also evaluated in bioequivalence study PAR-C10-005.

As of the interim data cutoff, the mean extent of exposure to Natpara administered with the Natpara Q-Cliq injector pen in RACE was 512.2 days. Across all Efficacy and Safety Studies in Hypoparathyroidism, mean exposure to the Ypsomed pen ranged from 57.2 days to 235.4 days.

There were 19 complaints (0.081 complaints per 100 injections) associated with use of the Natpara Q-Cliq and 108 complaints (0.286 complaints per 100 injections) associated with use of the Ypsomed pen (Table 56). For the Ypsomed pen, the majority of complaints were dose counter problems (25 complaints), dose activator problems (21 complaints), leaking medication (18 complaints), and cartridge problems (16 complaints). For the Natpara Q-Cliq, the most common complaints were leaking medication (5 complaints) and dose knob problems (3 complaints); all complaints for the Natpara Q-Cliq were determined to be use errors. All other specific complaints for the Natpara Q-Cliq were reported no more than 2 times.

Overall, 57.7% (56/97) of subjects reported 346 adverse events of any kind (related and not related to pen complaints) over 68.86 subject-years of exposure (502.5 events per 100 subject-years) while using the Natpara Q-Cliq compared to 77.5% (155/200) of subjects (including 50 healthy volunteers enrolled in the bioequivalence study,

PAR-C10-005) who reported 1401 events over 105.45 subject-years of exposure (1328.6 events per 100 subject-years) while using the Ypsomed pen. Of these, there were 24 events of injection site reaction (PTs of injection site hematoma, erythema, hemorrhage, pain, anaesthesia, rash and swelling) compared to 2 events reported by subjects while using the Natpara Q-Cliq.

Treatment-emergent adverse events with a proximal association to pen complaints were reviewed to assess if there was a possible association of events to pen complaints. Any event fitting this criterion was reported as potentially related to pen usage. Ten of 200 subjects reported 30 such events (i.e., possibly related TEAEs) for the Ypsomed pen (28.4 per 100 subject-years) vs. 1 of 97 subjects who reported 1 event with the Natpara Q-Cliq (1.5 per 100 subject-years). There were no potentially-related injection site reactions associated with pen complaints reported for either injection pen.

The risk management plan describes the distribution plan for Natpara and is intended to provide risk mitigation measures (Section 7.2). This includes a nurse visiting the patient's home to deliver the pen and to teach the patient how to prepare and administer Natpara, a follow-up nursing visit on Day 15 to enforce proper technique for changing the Natpara cartridge, and the availability of a trained pen specialist 24/7. NPS will be monitoring the distribution of Natpara, ensuring that a patient is trained prior to using Natpara Q-Cliq.

Table 56. Injection Pen Complaint by Reason – Safety Population – Studies C09-002, PAR C10-005, REPLACE, RELAY, RACE, and REPEAT

	Pen Type[a]					
	Ypsomed Pen N=200		Natpara Q-Cliq N=97		All Subjects N=200	
Reason	Events (%)[b]	Events per 100 injections[c]	Events (%)[b]	Events per 100 injections[c]	Events (%)[b]	Events per 100 injections[c]
Total	108 (100)	0.286	19 (100)	0.081	127 (100)	0.207
Dose Counter Problems	25 (23.1)	0.066	0	0	25 (19.7)	0.041
Reported Leaking Medication	18 (16.7)	0.048	5 (26.3)	0.021	23 (18.1)	0.037
Dose Activator Problems	21 (19.4)	0.056	0	0	21 (16.5)	0.034
Cartridge Problems	16 (14.8)	0.042	1 (5.3)	0.004	17 (13.4)	0.028
Daisy Tip Problems	7 (6.5)	0.019	0	0	7 (5.5)	0.011
Dose Switch Problems	4 (3.7)	0.011	0	0	4 (3.1)	0.007
Liquid Does not Come out	4 (3.7)	0.011	0	0	4 (3.1)	0.007
Misc (Supply Issue, N/A)	4 (3.7)	0.011	0	0	4 (3.1)	0.007
Needle-Related Problems	3 (2.8)	0.008	1 (5.3)	0.004	4 (3.1)	0.007
Dose Knob Problems	0	0	3 (15.8)	0.013	3 (2.4)	0.005
SC Retracted Complaint	3 (2.8)	0.008	0	0	3 (2.4)	0.005
Injection Button	0	0	2 (10.5)	0.008	2 (1.6)	0.003
Insufficient Details to Evaluate	2 (1.9)	0.005	0	0	2 (1.6)	0.003
Piston Rod-Related	0	0	2 (10.5)	0.008	2 (1.6)	0.003
Recon Device-Related Problems	0	0	2 (10.5)	0.008	2 (1.6)	0.003
Difficulty Attaching Cartridge to Pen Injector Base	0	0	1 (5.3)	0.004	1 (0.8)	0.002
Other	1 (0.9)	0.003	0	0	1 (0.8)	0.002
Stability or Form Change	0	0	1 (5.3)	0.004	1 (0.8)	0.002

Table 56. Injection Pen Complaint by Reason – Safety Population – Studies C09-002, PAR C10-005, REPLACE, RELAY, RACE, and REPEAT

	Pen Type[a]					
	Ypsomed Pen N=200		Natpara Q-Cliq N=97		All Subjects N=200	
Reason	Events (%)[b]	Events per 100 injections[c]	Events (%)[b]	Events per 100 injections[c]	Events (%)[b]	Events per 100 injections[c]
Stoppers Resist Meeting (push apart)	0	0	1 (5.3)	0.004	1 (0.8)	0.002
CMO/Packaging	0	0	0	0	0	0
Pen Jammed	0	0	0	0	0	0

CMO = contract manufacturing organization; N = number of subjects included in the safety population and received the specific pen type; N/A = not applicable; SC = study coordinator

a. Subjects from C09-002, REPLACE, RELAY, and REPEAT used Ypsomed pen; subjects from PAR-C10-005 and RACE used Ypsomed or/and Natpara Q-Cliq pens.
b. Percentages are based on the total number of injection pen complaints.
c. Number of events and event rate per 100 injections (defined as 100 x number of events/number of injections) are presented.

6.4.5 Immunogenicity

The formation of antibodies to PTH was assessed in the NPS clinical studies in hypoparathyroidism and osteoporosis. Since the active pharmaceutical ingredient of rhPTH(1-84) is manufactured using a strain of *E. coli*, there is potential for formation of antibodies to *E. coli* protein (ECP) as well.

Efficacy and Safety Studies in Hypoparathyroidism

In the clinical studies in hypoparathyroidism, 14 of 87 unique subjects with hypoparathyroidism treated with Natpara developed positive specific antibodies to PTH, based on the Meso-Scale Discovery method of analysis. None of these subjects had a systemic hypersensitivity reaction or any immunogenicity-related event related to Natpara treatment, or experienced loss of treatment effect.

In REPLACE, 3 Natpara-treated subjects and 1 placebo-treated subject developed specific antibodies to PTH at Week 24 or Week 28. In RELAY, 3 subjects previously treated with Natpara and 2 subjects previously not treated or treated with placebo had specific antibodies at baseline. Three of these subjects (2 previously treated with study drug, 1 previously not treated) remained positive at Week 8 (EOS). In REPEAT, 5 subjects had specific antibodies at Week 24 (EOS). Two of these were specific at Week 24, but not at Week 28 of REPLACE and 3 were positive/non-specific or negative at these 2 time points in the REPLACE. A total of 5 subjects in RACE were reported to have positive/specific antibodies. One incidence of neutralizing antibodies (in REPEAT) has been reported.

One subject with specific antibodies to PTH in REPLACE had an injection site reaction. This subject developed positive specific antibodies to PTH by Week 28 (4 weeks poststudy) in REPLACE. The subject experienced moderate injection site bruising (PT of injection site hematoma) that began 2 weeks after initiating study drug and shortly after up-titration to Natpara 75 µg/day. The subject was told to rotate injection sites and avoid Advil®. The injection site hematoma decreased to mild intensity, 3 weeks following these instructions, concurrently with a second up-titration to 100 µg/day. The mild injection site bruising and hematoma persisted until EOT. This subject subsequently enrolled in RACE without further events of injection site reactions.

One subject developed specific antibodies when participating in the open-label extension study, RACE. This subject had mild hives in REPLACE on Study Day 7 (7 days before randomization) that were considered not related to study drug and resolved with administration of diphenhydramine. When this subject enrolled in RACE, hives were not reported. This subject also developed a severe anaphylactic reaction to magnetic resonance imaging dye during RACE (not related to Natpara) that resolved. At Month 24 in the extension of RACE, this subject developed positive/specific antibodies to PTH. There was no recurrence of hives and no report of any other immunogenicity-related event or hypocalcemia.

One subject developed positive specific antibodies to PTH with neutralizing activity. This subject had positive specific antibodies at Week 24 in REPLACE and continued another 24 weeks in REPEAT where he had neutralizing antibodies on the last visit. He met the primary efficacy endpoint in both studies.

Efficacy and Safety Studies in Osteoporosis

In the studies in osteoporosis, 2 subjects who developed specific antibodies to PTH had mild hives and 1 subject who developed specific antibodies to PTH had a mild rash at the injection site for 1 day. There were no other immunogenicity-related events associated with the rhPTH(1-84).

Overall Summary

In summary, to date, there is no evidence of immune-mediated systemic hypersensitivity events related to Natpara in any subjects who had PTH-specific antibodies, neutralizing antibodies, or in subjects without these antibodies. There are no recommended changes to treatment based on the presence of these antibodies.

6.4.6 Osteosarcoma

As summarized in Section 3.2.3, the carcinogenicity study in rats found that the systemic exposure to rhPTH(1-84) at the no-carcinogenic effect dose was 3.3- to 4.8-fold greater (based on AUC) than the exposure observed in hypoparathyroidism subjects at the clinical dose of 100 µg/day. Focal osteoblast hyperplasia (FOH) has been described as part of the morphologic continuum associated with chronic administration of rhPTH(1-34) to the rat (Vahle et al., 2002). In the rat study with rhPTH(1-84), the no effect dose not associated with osteosarcoma was also not associated with other benign bone tumors and no change in the frequency of FOH, relative to control groups. The lowest dose at which osteosarcoma was not observed occurred at an exposure margin that was 19.2 (females) to 26.0 (males) higher than exposure at the highest clinical dose of 100 µg/day.

Teriparatide (rhPTH[1-34]) was also associated with the formation of osteosarcomas in the Fischer 344 (F344) strain of rats at all dose levels tested (5, 30, 75 µg/kg) (Vahle et al., 2002) and carries a boxed warning of this neoplastic effect in the product labeling. A more recent study from Japan in the Sprague-Dawley strain of rats also described a dose- and time-dependent induction of osteosarcomas following treatment with teriparatide for 2 years (Watanabe et al., 2012). However, because lower doses were evaluated (1.5, 4.5, 13.6 µg/kg), the authors were able to identify the 4.5 µg/kg dose as being non-carcinogenic. In contrast, a 5 µg/kg dose resulted in a 5-7% incidence of osteosarcomas in F344 rats (Vahle et al., 2002). A weekly 40.7 µg/kg dose did not induce osteosarcoma formation in Sprague-Dawley rats, but it also had only a small positive impact on bone mineral content (BMC) or bone mineral density when compared with daily injections (Watanabe et al., 2012).

Spontaneously occurring bone neoplasms are uncommon-to-rare in the Fischer 344 rat (Leininger and Riley, 1990; Litvinov and Soloviev, 1973; NTP, 2003). Incidences of bone neoplasms are observed in this rat species with rhPTH(1-84) and rhPTH(1-34), however, the relevance of the effect to humans is unknown. Fundamental differences exist in bone physiology between rats and humans (Vahle et al., 2002). Bone remodeling and turnover is greater in rats than humans making the extrapolation of a finding to human exposure is difficult since the rat is more sensitive.

Osteoanabolic effects of rhPTH(1-84) have also been extensively studied in cynomolgus macaque monkeys. Osteosarcoma has not developed in this non-human primate with exposure up to 25 µg/kg/day of PTH(1-84) for up to 18 months of treatment and 36 months of observation. These data seem to indicate much less sensitivity to an oncogenic effect of high-dose PTH in non-human primates, which may have more direct relevance to human subjects, than lower animal forms such as rats. There also have been no reported skeletal malignancies in any clinical trials in human subjects or cancer registries in human subjects, and epidemiological data suggest that mortality rates from cancer in primary hyperparathyroidism are actually lower than in control populations (Capriani et al., 2012). Long-term studies of 16 to 18 months' duration in monkeys have not detected any evidence of osteosarcoma or other bone proliferative lesions, either with rhPTH(1-84) or rhPTH(1-34) (Vahle et al., 2006; Jerome et al., 2001) or rhPTH(1-84) (Fox et al., 2007).

With respect to a possible mechanistic explanation for the differences in carcinogenic response with rhPTH(1-84) and rhPTH(1-34), an experimental study was conducted in rats treated with both materials. rhPTH(1-34) was a more effective stimulator of the proliferation of osteoblast progenitors and bone formation than rhPTH(1-84) at the same nmol/kg dose, despite similar increases in osteoblast numbers (Study PH04-025). Additionally, it was suggested that rhPTH(1-84) reduces osteoblast apoptosis and/or promotes differentiation of osteoblast precursors (via a pathway that does not require cell division) to a greater extent than PTH(1-34). It is possible that increased osteoblast formation may play a role in the greater induction of osteosarcoma in rats treated with rhPTH(1-34) when compared with rhPTH(1-84).

Radiographic analysis resulted in the detection of occult neoplasms that accounted for approximately 10% of the total neoplasms identified in the 2-year rat study with rhPTH(1-84). In comparison, radiography was not used in the rhPTH(1-34) carcinogenicity studies (Vahle et al., 2002; Vahle et al., 2004). As a result, the rhPTH(1-34) studies may be less sensitive for the detection of bone neoplasms when compared to the rhPTH(1-84) carcinogenicity study. Following 24 months of treatment, a no-carcinogenic effect dose was established for rhPTH(1-84), but this was not the case for rhPTH(1-34). However, when rhPTH(1-34) was administered to females for shorter durations, a no-carcinogenic effect dose was identified (i.e., 5 µg/kg/day). This study demonstrated that dose and duration of treatment were the most important factors in the induction of bone tumors with rhPTH(1-34) (Vahle et al., 2004).

There has also been significant long term post-marketing experience with rhPTH(1-34). Among the 430,000 people who have received rhPTH(1-34) since its initial introduction to the market in December 2002, 2 case reports were identified from the literature of osteosarcomas potentially occurring with rhPTH(1-34) therapy (Subbiah et al., 2010; Harper et al., 2007), although neither report provided conclusive evidence of the etiological role of rhPTH(1-34).

After 10 years of postmarketing experience with rhPTH(1-34) and 6 years with rhPTH(1-84) (Capriani et al., 2012), the absence of clinical or epidemiological reports conclusively linking these two treatments with the occurrence of osteosarcoma in humans questions the value of drawing any specific conclusions on the risk of osteosarcoma from the rat model. Moreover, interim 7-year results of a 15-year postmarketing surveillance study on 1448 adult patients with osteosarcoma in the United States found no evidence of prior use of rhPTH(1-34) (Andrews et al., 2012). Additional support for the lack of an association with osteosarcoma comes from a retrospective study of the possible relationship between osteosarcoma and primary hyperparathyroidism, which found that the prevalence of primary hyperparathyroidism in patients with osteosarcoma is not significantly different from that of the general population (Jimenez et al., 2005). In addition, there is no substantive evidence of osteosarcoma induction in clinical states of very high, prolonged PTH secretion, such as renal osteodystrophy (Hodsman et al., 2005).

Taken together, the published literature evaluating the use of rhPTH(1-84) support the safety conclusions from the Natpara development program, indicating that the product is generally safe and well tolerated, with no evidence of osteosarcoma reported in clinical trials or in over 6 years of postmarketing experience. In the case of rhPTH(1-34), evidence of an association with osteosarcoma exists in one animal species (rat), but this has not been seen in other animal species (e.g., monkey), nor has any association with rhPTH(1-84) and osteosarcoma in humans been reported. This issue appears to be a species-specific finding, with no increase in osteosarcoma reported over the past 6+ (rhPTH[1-84]) or 10+ (rhPTH[1-34]) years of use in humans.

7 KEY ELEMENTS IN PROPOSED LABELING AND RISK MANAGEMENT PROGRAM

7.1 Proposed Labeling

Key elements of the proposed labeling are as follows:

Indications and Usage:

Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism.

Dosage and Administration:

- Once daily subcutaneous injection.
- Not for intravenous or intramuscular injection.
- Recommended starting dose of Natpara is 50 mcg once daily. Based on calcemic response, titrate Natpara doses at 2 to 4 week intervals upward to doses of 75 mcg and then 100 mcg. Downward titration to a minimum dose of 25 mcg can occur at any time.
- Monitor serum calcium concentrations and adjust exogenous calcium sources upon initiation, change, or discontinuation of Natpara treatment.

Warnings and Precautions:

- Hypercalcemia. There is a potential for hypercalcemia to occur during Natpara treatment, more often during titration. This can be avoided or minimized by following the recommended dosing and monitoring information.
- Hypocalcemia. There is a potential for hypocalcemia to occur during Natpara treatment or following sustained withdrawal of Natpara. Interruption or discontinuation of Natpara treatment should be accompanied by monitoring of serum calcium concentrations and increase in exogenous calcium as necessary.

7.2 Risk Management Plan

The risk of hypocalcemia following interruption or discontinuation of Natpara treatment has been identified in the NPS Risk Management Plan for this orphan population. The key premise of the NPS risk mitigation strategy for the use of Natpara/Natpara Q-Cliq is based on NPS' ability to train each individual patient to proficiency by a national healthcare professional (HCP) network (mostly nurses/healthcare providers) before first use and at second use of the Natpara Q-Cliq.

Key features of this risk mitigation strategy are highlighted below:

- Every patient is to be properly trained to proficiency individually (by an NPS team, mostly nurses/healthcare providers) on the use of the pen before the first injection (Day 1) and before the first change in cartridge/next reconstitution (Day

15). This plan removes from the process variations such as availability or ability of a HCP to train the patients.

- These nurses/healthcare providers will be scheduled and sent to a Natpara patient's home at Day 1 of initiation of their Natpara therapy and then again at Day 15 for a refresher training session; at Day 15 the patient will have an option to have the refresher training over the phone – as per Simulated Use Validation (Summative) Testing - but the face to face training will be encouraged (continued 24/7 telephone support will remain available at any time). NPS will utilize the training for proficiency assessment used in the Simulated Use Validation Testing of Natpara, with reporting and feedback mechanism to ensure these training sessions are completed and the patient is considered proficient in the mixing and administration of Natpara with the Q-Cliq.
- Additionally, if after the first training session the nurse (healthcare provider) does not feel that the patient is sufficiently trained, they can schedule additional daily home visits, as needed. A training kit that includes the actual device will be available for use by patients during the training sessions by the nurse.
- Each NPS nurse/healthcare provider who will conduct patients' training will each first be trained to ensure consistency. They will be tested and certified prior to them visiting and training a Natpara patient using the Training Manual used during Simulated Use Validation Testing (summative study) of Natpara.
- The pen, which is included in the starter-kit, will be delivered to the patient by the trainer during the first training visit, making it impossible for the patient to self-inject Natpara medication before being trained to proficiency on correct use of the Q-Cliq pen.

8 CONCLUSION

Hypoparathyroidism is a rare disease attributable to a deficiency or absence of PTH, with symptoms and metabolic findings attributable to loss of normal physiological PTH activity. PTH has critical physiological functions that include its central role in the tight control of serum calcium and, along with other factors (e.g., fibroblast-derived growth factor 23), serum phosphate concentration. In the kidney, PTH stimulates renal reabsorption of calcium and promotes phosphate excretion. PTH enhances the conversion of 25(OH)D to $1,25(OH)_2D$. PTH also enables normal bone mineral physiology.

The current standard of treatment for hypoparathyroidism is oral calcium and active vitamin D, which are prescribed to maintain serum calcium levels and minimize symptoms of hypocalcemia. However, oral calcium and active vitamin D do not address the underlying PTH deficiency, rendering patients subject to the physiologic consequences of hypercalciuria, hyperphosphatemia, and reduced bone turnover. Physiologically without PTH, any increase in serum calcium results in increased urinary calcium, which can lead to hypercalciuria. Active vitamin D increases phosphate absorption in the kidney, which in the absence of PTH results in hyperphosphatemia. The combination of raising serum calcium through supplementation with the occurrence of hyperphosphatemia, results in high calcium-phosphate product and long-term soft tissue deposition of calcium. Additionally, without the normal effects of PTH on bone, the bone structure becomes abnormal and bone mineral metabolism is impaired, hindering the ability to mobilize calcium from bone.

Over the course of this chronic disease, patients accumulate longer-term sequelae due to the absence of PTH and the complications of oral calcium supplementation. Thus, there is medical necessity for a treatment of hypoparathyroidism that restores PTH activity and directly addresses the underlying disease and its physiologic effects. NPS developed Natpara as hormone replacement therapy to address these needs.

The pharmacodynamic properties of rhPTH(1-84), a recombinant human PTH that is manufactured using a strain of *E. coli* modified by recombinant DNA technology, were investigated across a number of studies (Table 57). The findings confirm that Natpara produces the expected physiological responses, including maintenance of serum calcium, decreased serum phosphate concentration, and reduction in hypercalciuria in hypoparathyroidism patients, while significantly decreasing the requirement for oral calcium and active vitamin D. Mean serum total calcium reaches its peak concentration between 10 and 12 hours following SC injection of Natpara and is sustained over baseline for more than 24 hours after administration. A once daily dose of Natpara provides an appropriate 24-hour calcemic response in hypoparathyroidism patients (while decreasing the requirement for oral calcium and active vitamin D).

Table 57. Summary of the Evidence of Physiological Changes Following Administration of Natpara – NPS Hypoparathyroidism Program

	REPLACE	RELAY	RACE	REPEAT	C09-002
Duration	**24 weeks**	**8 weeks**	**2 year**	**24 weeks**	**2 single doses**
Increased serum calcium concentrations	√	√	√	√	√
Increased renal calcium reabsorption	√	√	√	√	√
Decreased serum phosphate	√		√	√	√
Decreased calcium-phosphate product	√	√	√	√	
Endogenous 1,25-dihydroxyvitamin D production	√		√		√
Increased bone turnover	√	√	√[a]	√	
Decreased bone mineral density	√		√	√	

a. 1-year data

The REPLACE study confirmed that Natpara is superior to placebo and effective to maintain serum calcium with reduction in oral calcium and active vitamin D doses. The study consisted of an optimization baseline period during which calcium and active vitamin D therapies were optimized to achieve a clinically acceptable, stable, serum ACSC concentration with stabilized therapy. Following randomization to Natpara or placebo, titration of study drug and protocol-guided reduction in active vitamin D and calcium doses occurred during an 8-week titration period, which was followed by a maintenance period. Efficacy was assessed at 24 weeks.

A subject met the triple endpoint only if he/she achieved all of the following at the end of treatment:

- at least a 50% reduction from the baseline oral calcium dose, and
- at least a 50% reduction from the baseline active vitamin D dose, and
- an ACSC concentration that was maintained within a range of 7.5 to 10.6 mg/dL.

Each component in the response definition represented an endpoint of clinical significance. The minimum 50% reduction in calcium and active vitamin D is substantial given the dosing levels that many patients with hypoparathyroidism must maintain to control serum calcium levels.

Subjects assigned to Natpara had a significant treatment effect when compared to subjects assigned to placebo. Overall, 54.8% in the Natpara group met the primary endpoint compared to 2.5% in the placebo group ($p < 0.001$). Results of secondary (first 2 of 3) and prespecified exploratory endpoints confirmed Natpara activity in REPLACE.

The REPLACE design was conservative in assessing whether patients met the primary endpoint by requiring an early response on study without the opportunity for a more prolonged titration effort as could occur in standard medical practice. Since the protocol

did not permit titration of study drug dose after 8 weeks and the majority of changes to calcium or active vitamin D were to be completed by 12 weeks, such that the stable maintenance period would allow for careful assessment of efficacy, investigators did not have much time to titrate to effect. This constraint will not be mirrored in clinical practice; clinicians will titrate Natpara on an individualized basis, while calcium and active vitamin D doses are being reduced.

Long-term experience with Natpara was also examined in the RACE study (1 year; plus ongoing extension), affirming that the PTH activity of Natpara continues with long-term treatment.

The overall safety experience with Natpara in the hypoparathyroidism and osteoporosis clinical development programs as well as in significant osteoporosis postmarketing experience supports the overall safety. Two risks have been identified: hypercalcemia during the initial titration period and hypocalcemia, especially after complete and sustained withdrawal of Natpara. These events are manageable by measuring serum calcium concentration during the titration phase or in the setting of complete, sustained withdrawal and adjusting Natpara dosing and calcium and active vitamin D supplementation accordingly. No unique findings were reported in the osteoporosis development program or postmarketing experience, further reinforcing the safety profile of Natpara.

In summary, Natpara addresses an unmet medical need in hypoparathyroidism for a treatment to restore the activity of endogenous PTH. Natpara is a well-tolerated, hormone replacement treatment for hypoparathyroidism patients that maintains serum calcium, reduces or eliminates the need for oral calcium and active vitamin D, and provides positive physiologic effects on rates of hypercalciuria, reduction of hyperphosphatemia, and returns abnormal bone metabolism toward normal. The results of the development program support the approval of Natpara for the long-term treatment of patients with hypoparathyroidism.

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10 APPENDICES

10.1 Appendix A. Summary Tables for Efficacy and Safety Studies in Osteoporosis

Table 58. Listing of Efficacy and Safety Studies in Osteoporosis

Study Number	Primary Objectives	Study Design and Type of Control	Test Product(s), Number of Subjects[a]	Status of Subjects	Duration of Treatment
Placebo-controlled studies					
ALX1-11-93001 (TOP)	Efficacy (vertebral fracture incidence) and safety	Randomized, double-blind, placebo-controlled	Placebo, 1246 100 µg rhPTH(1-84), 1286[b]	Postmenopausal women with osteoporosis	18 months
ALX1-11-821	Efficacy (BMD) and safety	Dose-finding, randomized, double-blind, placebo-controlled	Placebo, 55 50 µg rhPTH(1-84), 52 75 µg rhPTH(1-84), 55 100 µg rhPTH(1-84), 55	Postmenopausal women with osteoporosis	12 months
CL1-11-008 (CAP)	Efficacy (BMD) and Safety	Randomized, double-blind, placebo-controlled	100 µg rhPTH(1-84)+ calcium + vitamin D_3, 123 100 µg rhPTH(1-84)+ placebo + vitamin D_3, 126 Placebo + calcium + vitamin D_3, 125	Postmenopausal women with osteoporosis	6 months
Active-controlled Studies					
CL1-11-003 (POWER)	Efficacy (BMD) and safety	Randomized, double-blind, active-controlled, combination therapy	HRT + placebo, 90 HRT + 100 µg rhPTH(1-84), 90	Postmenopausal women with low bone mass on stable HRT	24 months (Study concluded early at 18 months)

Table 58. Listing of Efficacy and Safety Studies in Osteoporosis

Study Number	Primary Objectives	Study Design and Type of Control	Test Product(s), Number of Subjects[a]	Status of Subjects	Duration of Treatment
N01-AR-9-2245 (PaTH) Sponsored by NIH	Efficacy (BMD) and safety	Randomized, double-blind, active-controlled, combination therapy	**Year 1:** 100 µg PTH + placebo,119 10 mg ALN + placebo, 60 100 µg PTH + 10 mg ALN, 59 **Year 2:** 100 µg PTH/placebo, 53 10 mg ALN/10 mg ALN, 56 100 µg PTH + 10 mg ALN/ 10 mg ALN, 55 100 µg PTH/ 10 mg ALN, 50	Postmenopausal women with osteoporosis	24 months (PTH administered only in the first 12 months)
Uncontrolled studies					
CL1-11-002 (OLES; Extension to TOP)	Efficacy (BMD) and Safety	Open-label extension study	Placebo /100 µg PTH, 900 100 µg PTH/100 µg PTH, 781	Postmenopausal women with osteoporosis	18 months[b]
CL1-11-016 (TRES; Extension to OLES)	Efficacy (BMD) and Safety	Open-label extension study	Placebo/100 µg PTH/ 100 µg PTH, 98	Postmenopausal women with osteoporosis	18 months[c]

ALN = alendronate; BMD = bone mineral density; CAP = calcium supplementation study; HRT = hormone replacement therapy; NIH = National Institute of Health; OLES = open-label extension study; PaTH = PTH and alendronate; POWER = PTH osteoporotic women on estrogen replacement; PTH = parathyroid hormone;TOP = treatment of osteoporosis with parathyroid hormone; TRES = treatment extension study.

a. Substudies were comprised of a subset of subjects.
b. Subjects may have been treated with rhPTH(1-84) for a total of up to 24 months (TOP and OLES [open-label extension study] combined.
c. Subjects treated with rhPTH(1-84) for up to 36 months (OLES and TRES combined)

Table 59. Demographics and Other Baseline Characteristics - Safety Population, Efficacy and Safety Studies in Osteoporosis

Parameter	rhPTH(1-84) alone (Any dose) N=2715	rhPTH(1-84) in combination (Any dose) N=149	rhPTH(1-84) alone or in combination (Any dose) N=2864
Age at Screening (years)[a]			
n	2715	149	2864
Mean (SD)	64.7 (7.52)	62.6 (8.48)	64.6 (7.59)
Min, Max	45, 94	45, 82	45, 94
Sex, n (%)			
Female	2715 (100)	149 (100)	2864 (100)
Male	0	0	0
Race, n (%)			
White	2275 (83.8)	145 (97.3)	2420 (84.5)
Black	35 (1.3)	4 (2.7)	39 (1.4)
Asian	27 (1.0)	0	27 (0.9)
Native Hawaiian/ Pacific Islander	2 (0.1)	0	2 (0.1)
American Indian/ Native American	3 (0.1)	0	3 (0.1)
Other	373 (13.7)	0	373 (13.0)
Height (cm)			
n	2706	149	2855
Mean (SD)	157.20 (6.953)	159.70 (6.823)	157.33 (6.967)
Min, Max	108.9, 183.8	142.8, 179.6	108.9, 183.8
Weight (kg)			
n	2711	149	2860
Mean (SD)	63.21 (11.244)	64.50 (12.182)	63.27 (11.297)
Min, Max	40.0, 146.3	44.2, 123.2	40.0, 146.3
BMI (kg/m^2)			
n	2706	149	2855
Mean (SD)	25.60 (4.393)	25.32 (4.748)	25.58 (4.412)
Min, Max	15.4, 55.5	16.9, 50.4	15.4, 55.5
Geographic Region of Enrollment, n (%)			
North America	1829 (67.4)	59 (39.6)	1888 (65.9)
Western Europe	0	72 (48.3)	72 (2.5)
Central/Eastern Europe	172 (6.3)	18 (12.1)	190 (6.6)
Other	714 (26.3)	0	714 (24.9)

BMI = body mass index; Max = maximum; Min = minimum; N = number of subjects in the treatment group; n = number of subjects with non-missing baseline information; SD = standard deviation
Note: If a subject participated in more than one study, the demographic and baseline information from the first participated study for the integrated analysis group are presented. Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.
a. Age reflects the subject's age at the first screening leading to enrollment.

Table 60. Summary of the Most Frequently Reported (≥ 1% of rhPTH[1-84]-treated Subjects) On-treatment Treatment-emergent Adverse Events Leading to Drug Discontinuation - Safety Population, Efficacy and Safety Studies in Osteoporosis

	Placebo-controlled Studies in Osteoporosis[a]		Active-Controlled Studies in Osteoporosis[b]			Uncontrolled Studies in Osteoporosis[c]	Total Efficacy and Safety Studies in Osteoporosis[d]		
Preferred Term	Placebo N=1425 n (%)	rhPTH(1-84) alone (Any dose) N=1696 n (%)	rhPTH(1-84) alone (Any dose) N=119 n (%)	rhPTH(1-84) in combination (Any dose) N=149 n (%)	rhPTH(1-84) alone or in combination (Any dose) N=268 n (%)	rhPTH(1-84) alone (Any dose) N=1681 n (%)	rhPTH(1-84) alone (Any dose) N=2715 n (%)	rhPTH(1-84) in combination (Any dose) N=149 n (%)	rhPTH(1-84) alone or in combination (Any dose) N=2864 n (%)
Nausea	3 (0.2)	51 (3.0)	2 (1.7)	6 (4.0)	8 (3.0)	26 (1.5)	80 (2.9)	6 (4.0)	86 (3.0)
Headache	6 (0.4)	22 (1.3)	3 (2.5)	4 (2.7)	7 (2.6)	11 (0.7)	36 (1.3)	4 (2.7)	40 (1.4)
Hypercalciuria	11 (0.8)	22 (1.3)	0	3 (2.0)	3 (1.1)	12 (0.7)	36 (1.3)	3 (2.0)	39 (1.4)

N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TEAE = treatment-emergent adverse event.
Note: On-treatment TEAE or TEAE with an outcome of death that occurred within 30 days after the last treatment received that led to drug discontinuation are included in this table. The Total columns may include between-study adverse events; hence the overall counts may not equal to the sum of individual studies.
a. Placebo-controlled Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, and CL1-11-008.
b. Active-Controlled Studies in Osteoporosis include: N01-AR-9-2245 and CL1-11-003.
c. Uncontrolled Studies in Osteoporosis include: CL1-11-002 and CL1-11-016.
d. Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

Table 61. Summary of Most Frequently Reported (≥ 5% of Total rhPTH(1-84)-treated Subjects) On-treatment Treatment-emergent Adverse Events - Safety Population, Efficacy and Safety Studies in Osteoporosis

	Placebo-controlled Studies in Osteoporosis[a]		Active Controlled Studies in Osteoporosis[b]			Uncontrolled Studies in Osteoporosis[c]	Total Efficacy and Safety Studies in Osteoporosis[d]		
Preferred Term	**Placebo N=1425 n (%)**	**rhPTH(1-84) alone (Any dose) N=1696 n (%)**	**rhPTH(1-84) alone (Any dose) N=119 n (%)**	**rhPTH(1-84) in combination (Any dose) N=149 n (%)**	**rhPTH(1-84) alone or in combination (Any dose) N=268 n (%)**	**rhPTH(1-84) alone (Any dose) N=1681 n (%)**	**rhPTH(1-84) alone (Any dose) N=2715 n (%)**	**rhPTH(1-84) in combination (Any dose) N=149 n (%)**	**rhPTH(1-84) alone or in combination (Any dose) N=2864 n (%)**
Hypercalciuria	301 (21.1)	680 (40.1)	7 (5.9)	48 (32.2)	55 (20.5)	556 (33.1)	1170 (43.1)	48 (32.2)	1218 (42.5)
Hypercalcaemia	55 (3.9)	388 (22.9)	15 (12.6)	19 (12.8)	34 (12.7)	325 (19.3)	703 (25.9)	19 (12.8)	722 (25.2)
Headache	326 (22.9)	473 (27.9)	16 (13.4)	42 (28.2)	58 (21.6)	219 (13.0)	671 (24.7)	42 (28.2)	713 (24.9)
Nausea	122 (8.6)	343 (20.2)	17 (14.3)	33 (22.1)	50 (18.7)	214 (12.7)	548 (20.2)	33 (22.1)	581 (20.3)
Arthralgia	253 (17.8)	283 (16.7)	23 (19.3)	26 (17.4)	49 (18.3)	194 (11.5)	482 (17.8)	26 (17.4)	508 (17.7)
Back pain	278 (19.5)	281 (16.6)	15 (12.6)	28 (18.8)	43 (16.0)	182 (10.8)	458 (16.9)	28 (18.8)	486 (17.0)
Nasopharyngitis	229 (16.1)	246 (14.5)	14 (11.8)	19 (12.8)	33 (12.3)	165 (9.8)	399 (14.7)	19 (12.8)	418 (14.6)
Pain in extremity	207 (14.5)	213 (12.6)	19 (16.0)	13 (8.7)	32 (11.9)	148 (8.8)	368 (13.6)	13 (8.7)	381 (13.3)
Influenza	168 (11.8)	193 (11.4)	7 (5.9)	12 (8.1)	19 (7.1)	119 (7.1)	303 (11.2)	12 (8.1)	315 (11.0)
Dizziness	110 (7.7)	181 (10.7)	14 (11.8)	13 (8.7)	27 (10.1)	104 (6.2)	295 (10.9)	13 (8.7)	308 (10.8)
Diarrhoea	109 (7.6)	136 (8.0)	9 (7.6)	8 (5.4)	17 (6.3)	73 (4.3)	214 (7.9)	8 (5.4)	222 (7.8)
Dyspepsia	99 (6.9)	112 (6.6)	10 (8.4)	11 (7.4)	21 (7.8)	85 (5.1)	200 (7.4)	11 (7.4)	211 (7.4)
Hypertension	96 (6.7)	109 (6.4)	3 (2.5)	3 (2.0)	6 (2.2)	95 (5.7)	203 (7.5)	3 (2.0)	206 (7.2)
Urinary tract infection	88 (6.2)	102 (6.0)	5 (4.2)	12 (8.1)	17 (6.3)	83 (4.9)	184 (6.8)	12 (8.1)	196 (6.8)
Fatigue	79 (5.5)	116 (6.8)	11 (9.2)	6 (4.0)	17 (6.3)	63 (3.7)	188 (6.9)	6 (4.0)	194 (6.8)
Vomiting	59 (4.1)	117 (6.9)	0	11 (7.4)	11 (4.1)	68 (4.0)	180 (6.6)	11 (7.4)	191 (6.7)
Injection site haematoma	91 (6.4)	135 (8.0)	12 (10.1)	6 (4.0)	18 (6.7)	31 (1.8)	176 (6.5)	6 (4.0)	182 (6.4)
Muscle spasms	80 (5.6)	101 (6.0)	9 (7.6)	10 (6.7)	19 (7.1)	65 (3.9)	169 (6.2)	10 (6.7)	179 (6.3)

Table 61. Summary of Most Frequently Reported (≥ 5% of Total rhPTH(1-84)-treated Subjects) On-treatment Treatment-emergent Adverse Events - Safety Population, Efficacy and Safety Studies in Osteoporosis

	Placebo-controlled Studies in Osteoporosis[a]		Active Controlled Studies in Osteoporosis[b]			Uncontrolled Studies in Osteoporosis[c]	Total Efficacy and Safety Studies in Osteoporosis[d]		
Preferred Term	**Placebo N=1425 n (%)**	**rhPTH(1-84) alone (Any dose) N=1696 n (%)**	**rhPTH(1-84) alone (Any dose) N=119 n (%)**	**rhPTH(1-84) in combination (Any dose) N=149 n (%)**	**rhPTH(1-84) alone or in combination (Any dose) N=268 n (%)**	**rhPTH(1-84) alone (Any dose) N=1681 n (%)**	**rhPTH(1-84) alone (Any dose) N=2715 n (%)**	**rhPTH(1-84) in combination (Any dose) N=149 n (%)**	**rhPTH(1-84) alone or in combination (Any dose) N=2864 n (%)**
Upper respiratory tract infection	89 (6.2)	97 (5.7)	5 (4.2)	12 (8.1)	17 (6.3)	61 (3.6)	156 (5.7)	12 (8.1)	168 (5.9)
Cough	79 (5.5)	97 (5.7)	6 (5.0)	7 (4.7)	13 (4.9)	57 (3.4)	160 (5.9)	7 (4.7)	167 (5.8)
Abdominal pain upper	87 (6.1)	95 (5.6)	1 (0.8)	10 (6.7)	11 (4.1)	63 (3.7)	156 (5.7)	10 (6.7)	166 (5.8)
Constipation	93 (6.5)	100 (5.9)	10 (8.4)	12 (8.1)	22 (8.2)	44 (2.6)	148 (5.5)	12 (8.1)	160 (5.6)
Insomnia	85 (6.0)	107 (6.3)	5 (4.2)	5 (3.4)	10 (3.7)	44 (2.6)	154 (5.7)	5 (3.4)	159 (5.6)
Bronchitis	86 (6.0)	71 (4.2)	3 (2.5)	2 (1.3)	5 (1.9)	81 (4.8)	152 (5.6)	2 (1.3)	154 (5.4)
Musculoskeletal pain	95 (6.7)	84 (5.0)	3 (2.5)	8 (5.4)	11 (4.1)	55 (3.3)	142 (5.2)	8 (5.4)	150 (5.2)
Sinusitis	78 (5.5)	84 (5.0)	7 (5.9)	6 (4.0)	13 (4.9)	54 (3.2)	143 (5.3)	6 (4.0)	149 (5.2)
Abdominal pain	83 (5.8)	93 (5.5)	1 (0.8)	6 (4.0)	7 (2.6)	54 (3.2)	142 (5.2)	6 (4.0)	148 (5.2)

N = number of subjects in the treatment group; n = number of subjects with specified events in the treatment group; TEAE = treatment-emergent adverse event.
Note: All on-treatment TEAE and TEAE with an outcome of death which occurred within 30 days after the last treatment received are included in this table. Data are presented by decreasing frequency in the rhPTH(1-84) alone or in combination group, Total Efficacy and Safety Studies in Osteoporosis.

a. Placebo controlled Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, and CL1-11-008.
b. Active Controlled Studies in Osteoporosis include: N01-AR-9-2245 and CL1-11-003.
c. Uncontrolled Studies in Osteoporosis include: CL1-11-002 and CL1-11-016.
d. Efficacy and Safety Studies in Osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

10.2 Appendix B. Listing of Deaths - Safety Population, Efficacy and Safety Studies in Osteoporosis

Treatment: Study Group: Study ID/ Unique Subject ID	Age/ Sex/ Race[a]	AE With an Outcome of Death System Organ Class/ Investigator Term/ MedDRA Preferred Term/ AE Group Term[b]	AE Onset Day/ AE Cumulative Exposure (days)[c]	Number of Days post treatment	Investigator's Assessment of Relationship of AE to Study Medication
Placebo: Efficacy and Safety Studies in Osteoporosis: ALX1-11-93001					
ALX1-11-93001-2020-0030*	76/ F/ W	Nervous system disorders/ CEREBROVASCULAR ACCIDENT/ Cerebrovascular accident/ NA	134/ NA	41	Not associated to study drug
ALX1-11-93001-7001-0204*	76/ F/ O	Cardiac disorders/ ACUTE MYOCARDIAL INFARCTION/ Acute myocardial infarction/ NA	442/ NA	86	Not associated to study drug
rhPTH(1-84) Alone (Any Dose): Efficacy and Safety Studies in Osteoporosis: ALX1-11-93001					
ALX1-11-93001-2001-0420*	74/ F/ W	Cardiac disorders/ MYOCARDIAL INFARCTION/ Myocardial infarction/ NA	350/ 350	65	Not associated to study drug
rhPTH(1-84) Alone (Any Dose): Efficacy and Safety Studies in Osteoporosis: N01-AR-9-2245					
N01-AR-9-2245-0001-1071*	72/ F/ W	General disorders and administration site conditions/ DEATH/ Death/ NA	417/ 417	93	No relation
		Nervous system disorders/ SLURRED SPEECH/ Dysarthria/ NA	417/ 417	93	-

Treatment: Study Group: Study ID/ Unique Subject ID	Age/ Sex/ Race[a]	AE With an Outcome of Death System Organ Class/ Investigator Term/ MedDRA Preferred Term/ AE Group Term[b]	AE Onset Day/ AE Cumulative Exposure (days)[c]	Number of Days post treatment	Investigator's Assessment of Relationship of AE to Study Medication
rhPTH(1-84) Alone (Any Dose): Efficacy and Safety Studies in Osteoporosis: N01-AR-9-2245					
N01-AR-9-2245-0004-4256*	65/ F/ W	General disorders and administration site conditions/ DEATH/ Death/ NA	257/ 257	255	-
		General disorders and administration site conditions/ DEATH/ Death/ NA	257/ 257	255	-
		General disorders and administration site conditions/ DEATH/ Death/ NA	257/ 257	255	No relation
		Infections and infestations/ CREUTZFELDT JAKOB DISEAS/ Creutzfeldt-Jakob disease/ NA	257/ 257	255	No relation
		Infections and infestations/ CREUTZFELDT JAKOB DISEASE/ Creutzfeldt-Jakob disease/ NA	257/ 257	255	-
rhPTH(1-84) Alone (Any Dose): Efficacy and Safety Studies in Osteoporosis: CL1-11-002					
ALX1-11-93001-1001-0040*	68/ F/ W	Nervous system disorders/ SUBARACHNOID HEMORRHAGE/ Subarachnoid haemorrhage/ NA	226/ 779	72	Not associated to study drug

Treatment: Study Group: Study ID/ Unique Subject ID	Age/ Sex/ Race[a]	AE With an Outcome of Death System Organ Class/ Investigator Term/ MedDRA Preferred Term/ AE Group Term[b]	AE Onset Day/ AE Cumulative Exposure (days)[c]	Number of Days post treatment	Investigator's Assessment of Relationship of AE to Study Medication
ALX1-11-93001-1011-0011*	72/ F/ W	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ CANCER RIGHT KIDNEY/ Renal cancer/ NA	76/ 76	31	Not associated to study drug
ALX1-11-93001-2020-0076	62/ F/ O	Cardiac disorders/ CARDIOVASCULAR ARREST DUE TO MI/ Myocardial infarction/ NA	248/ 248	1	Associated to study drug[d]
ALX1-11-93001-2107-0115	62/ F/ W	Blood and lymphatic system disorders/ DISSEMINATED INTRAVASCULAR COAGULATION/ Disseminated intravascular coagulation/ NA	71/ 616	15	Not associated to study drug
ALX1-11-93001-4001-0040	61/ F/ W	Infections and infestations/ SUSPICION OF LUNG INFECTION/ Lung infection/ NA	93/ 93	-	Not associated to study drug
		Respiratory, thoracic and mediastinal disorders/ PULMONARY THROMBEMBOLISM-CARDIAC FORM WITH LETHAL OUT COME/ Pulmonary embolism/ NA	101/ 101	5	Unknown relation to study drug
rhPTH(1-84) Alone (Any Dose): Efficacy and Safety Studies in Osteoporosis: CL1-11-002					
ALX1-11-93001-4004-0004	54/ F/ W	Vascular disorders/ AORTIC DESSECTING ANEURYSM/ Aortic dissection/ NA	212/ 212	-	Not associated to study drug

Treatment: Study Group: Study ID/ Unique Subject ID	Age/ Sex/ Race[a]	AE With an Outcome of Death System Organ Class/ Investigator Term/ MedDRA Preferred Term/ AE Group Term[b]	AE Onset Day/ AE Cumulative Exposure (days)[c]	Number of Days post treatment	Investigator's Assessment of Relationship of AE to Study Medication
ALX1-11-93001-6002-0036	62/ F/ O	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ OVARIAN CANCER/ Ovarian cancer/ NA	460/ 460	-	Not associated to study drug
ALX1-11-93001-6009-0003*	69/ F/ O	Cardiac disorders/ CARDIOPULMONARY ARREST/ Cardio-respiratory arrest/ NA	467/ 1030	285	Not associated to study drug
ALX1-11-93001-7001-0122	71/ F/ O	Infections and infestations/ PNEUMONIA LEADING TO SEPSIS/ Pneumonia/ NA	8/ 566	-	Not associated to study drug
		Infections and infestations/ PNEUMONIA LEADING TO SEPSIS/ Sepsis/ NA	8/ 566	-	Not associated to study drug
rhPTH(1-84) Alone (Any Dose): Efficacy and Safety Studies in Osteoporosis: CL1-11-002					
ALX1-11-93001-7001-0154	70/ F/ O	Metabolism and nutrition disorders/ HEPATIC METHATASES OF ADENOCARCINOMA WITH CAQUEXIA/ Cachexia/ NA	170/ 723	-	Not associated to study drug
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ HEPATIC METHATASES OF ADENOCARCINOMA WITH CAQUEXIA/ Metastases to liver/ NA	170/ 723	-	Not associated to study drug

Treatment: Study Group: Study ID/ Unique Subject ID	Age/ Sex/ Race[a]	AE With an Outcome of Death System Organ Class/ Investigator Term/ MedDRA Preferred Term/ AE Group Term[b]	AE Onset Day/ AE Cumulative Exposure (days)[c]	Number of Days post treatment	Investigator's Assessment of Relationship of AE to Study Medication
ALX1-11-93001-7001-0200*	76/ F/ W	General disorders and administration site conditions/ SUDDEN DEATH/ Sudden death/ NA	329/ 329	35	Not associated to study drug

A = Asian; AE = adverse event; B = Black; F = female; I = American Indian/Native American; M =male, MedDRA = Medical Dictionary for Regulatory Activities; N =-Native Hawaiian/Pacific Islander; NA = not applicable; O = other; U = not collected; W = white.
Notes: Subject ID's noted with an asterisk (*) denote subjects who experienced AEs (with outcome of death) after 30 days of receiving their last treatment.
a. Age (years) reflects the subject's age at the first screening leading to enrollment;
b. Adverse Event Groupings represent medically similar terms and are applied to Efficacy and Safety Studies in Hypoparathyroidism.
c. AE onset day = AE start date relative to the first dose of study medication (including placebo) in the study during which the AE was collected. AE cumulative exposure = the total number of days from the very first rhPTH(1-84) dose to AE onset, excluding treatment breaks between studies; 'NA' is displayed for AEs that occurred during placebo treatment period.
d. The investigator later reassessed the death of 1 subject as not associated with study drug and instead related to an underlying medical condition of coronary artery disease.